Introduction

(GENERAL PHARMACOLOGY)

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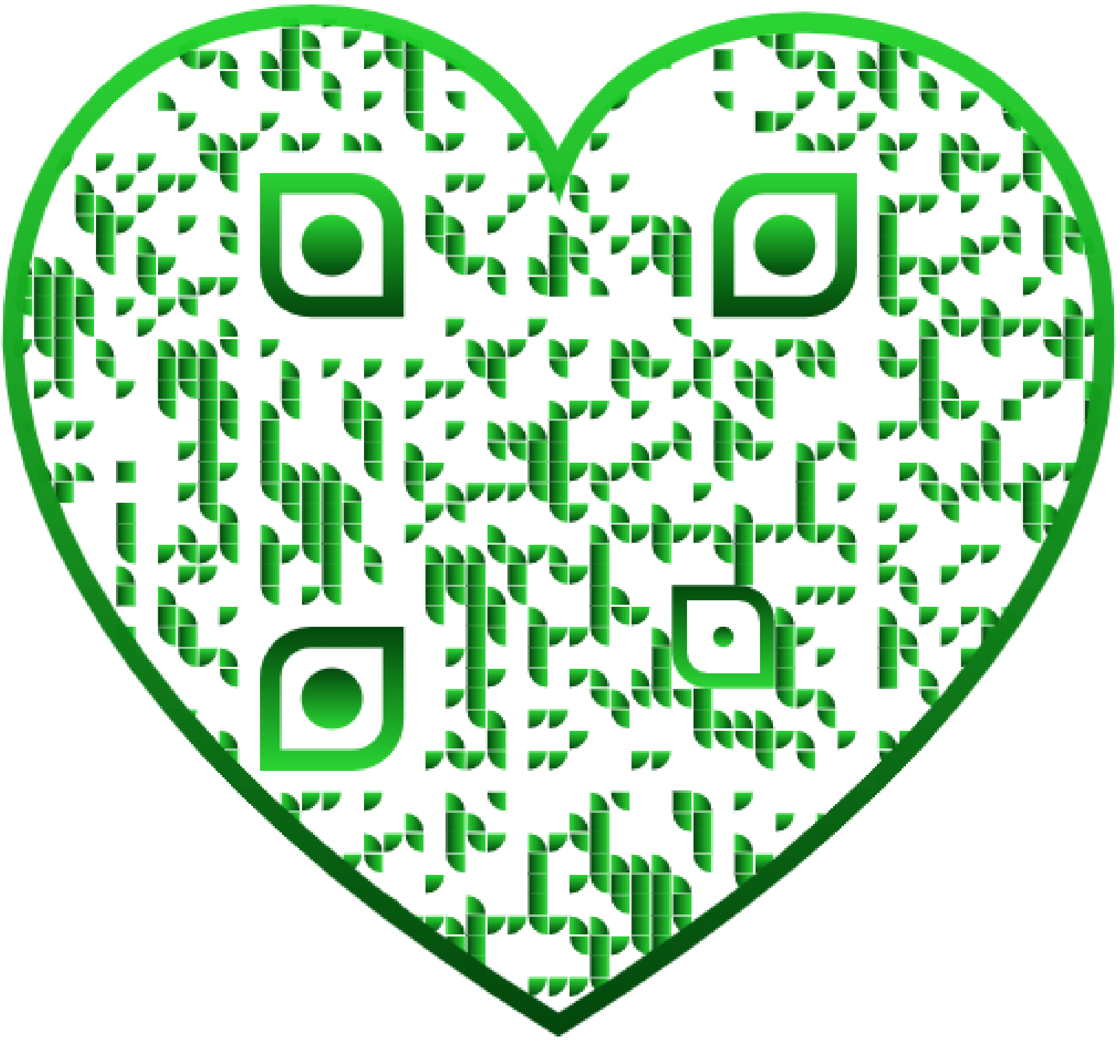


What is Pharmacology?

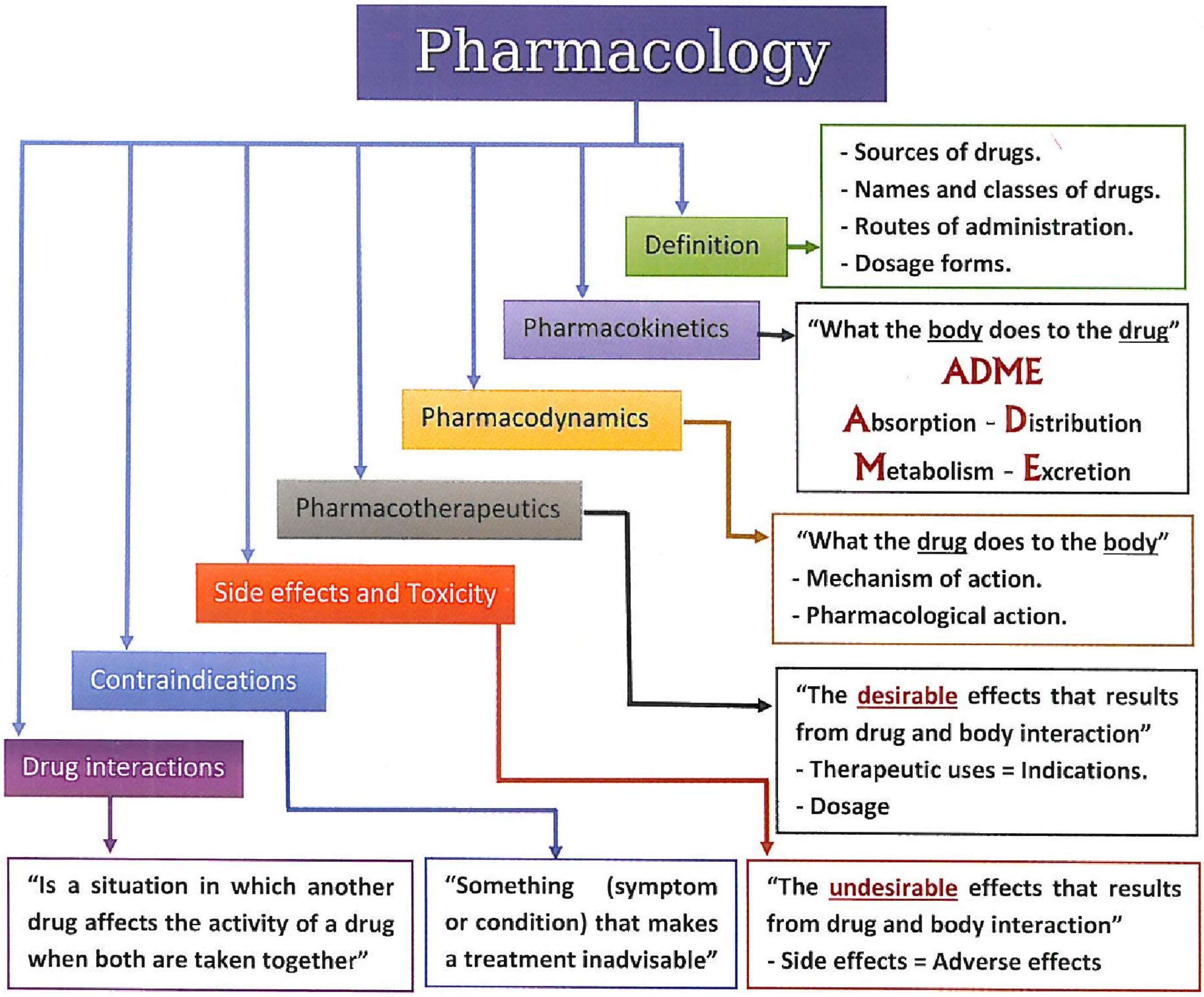
حمل احد برامج
QR Code Reader
من متجر جوجل بلاي او ابل ستور
افتح البرنامج وقم بقراءة الكود بواسطة
الكاميرا، ليتم تحويلك الى اليوتيوب
مباشرة لمشاهدة فيديو شرح الموضوع

➢ What is Pharmacology?

- It is the **science** *that* **deals** *with the* Study of **chemical substances** (**Drugs**).
- **Meaning of "**Study**" here:**

  - What they are? - How they work? - What they do?

> Note Book (N.B.);
>
> ***Toxicology***; is a ***branch*** of **pharmacology** which ***deals with*** the **undesirable effects** of **chemicals** and **drugs** ***on*** **living system**.



Pharmacology

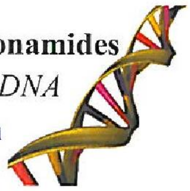
- **Definition** → - Sources of drugs. - Names and classes of drugs. - Routes of administration. - Dosage forms.
- **Pharmacokinetics** → "What the body does to the drug" **ADME**: **A**bsorption - **D**istribution - **M**etabolism - **E**xcretion
- **Pharmacodynamics** → "What the drug does to the body" - Mechanism of action. - Pharmacological action.
- **Pharmacotherapeutics** → "The desirable effects that results from drug and body interaction" - Therapeutic uses = Indications. - Dosage
- **Side effects and Toxicity** → "The undesirable effects that results from drug and body interaction" - Side effects = Adverse effects
- **Contraindications** → "Something (symptom or condition) that makes a treatment inadvisable"
- **Drug interactions** → "Is a situation in which another drug affects the activity of a drug when both are taken together"

➢ Drug (Therapeutic Agent):-

- Definition (Def.); *any* substance *other than* **food** *can be* **used** *in* **diagnosis**, **treatment** or **prevention** of a **disease**.
- Sources of drugs;

  1) **Natural sources**;
     - **Plant** e.g. **Pilocarpine**
     - **Animal** e.g. **Heparin**
     - **Microorganisms** e.g. **Antibiotics**
     - **Minerals** e.g. **Ferrous sulfate**

  2) **Synthetic sources**;
     - **Chemically** e.g. **Sulphonamides**
     - **Genetic engineering** (*rDNA technology*) e.g. **Insulin**



- **Names of drugs:**
  1) **Chemical name** e.g. **Acetylsalicylic Acid**
  2) **Generic name** e.g. **Aspirin**
  3) **Trade name** e.g. **Rivo®**
- **Classes of drugs:**
  1) **Prescription Only Medication (POM)**;
     - **Drug** that **legally** ***require*** a **medical prescription** *to be dispensed*.
  2) **Over The Counter (OTC) drugs**;
     - **Used** by the **public** ***without*** a **prescription**.
     - ***For example*** "e.g."; analgesics, laxative, antitussive and antacids.

Routes of Drug Administration

- **Oral**
- **Parenteral**
- **Mucosal**
- **Inhalation**
- **Topical**

1: Oral Route;

- **Advantage;**
  - **Safe** (overdose may be overcome).
  - ***Easily*** **self-administered** and **economic**.
  - **Non-irritant** (If mild irritant ⇨ Take after meal or use enteric coated form).
  - **Palatable** (If bad taste ⇨ Dilute with milk or fruit juice or use sugar coated form).
- **Disadvantage;**

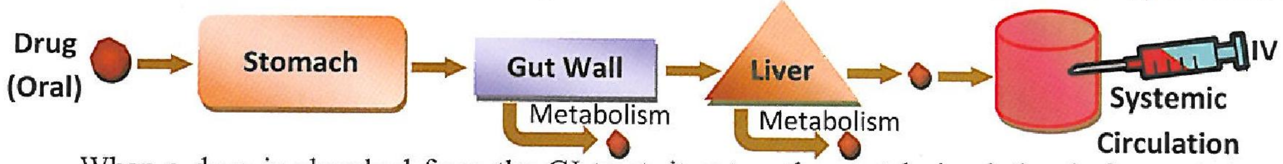
Not suitable for

- ***Excessive*** **vomiting** and **diarrhea**.
- **Emergencies** (Delayed onset of action).
- ***Very*** **irritant drugs** e.g. Emetine (Anti-amoebic).
- ***Unconscious*** and ***uncooperative*** **patients**.
- **Drugs** ***not*** **absorbed** *from* **gastrointestinal tract** (**GIT**) *when* **systemic effect** *is* **wanted** e.g. streptomycin in tuberculosis (TB).
- **Drugs** ***destroyed by*** **gastric acidity** e.g. **Benzyl penicillin**.
- **Drugs** ***destroyed by*** **digestive enzymes** e.g. **Insulin**.
- **Drugs** *with extensive* **first pass effect** e.g. **Lidocaine**.

****

1st pass effect or 1st pass hepatic metabolism or Pre-systemic metabolism

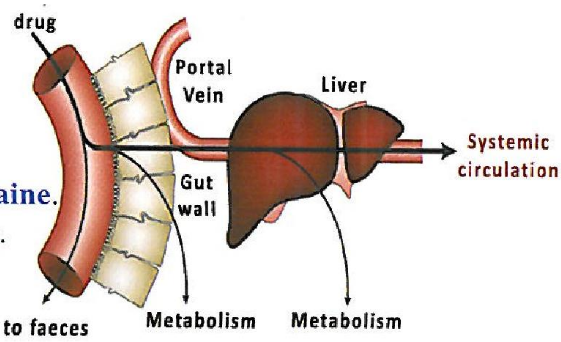
- **Def.**; is a ***phenomenon*** of **drug metabolism** *whereby* the ***concentration*** of a **drug** is ***greatly reduced*** *before* it ***reaches*** the **systemic circulation** ⇨ ***Decrease*** **bioavailability** of the **drug**.



- When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation.
- If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is *decreased*.

Bioavailability; is the **fraction (%)** of an **administered dose** of **unchanged drug** that ***reaches*** the **systemic circulation**. ***Bioavailability*** of **intravenous (IV) route = 100%**.

- **Sites;**
  1) **Gut first pass effect;**
     - **Gastric acidity** ⇨ **Benzyl penicillin.**
     - **Digestive enzyme** ⇨ **Insulin.**
     - **Mucosal enzyme** ⇨ **Tyramine.**
  2) **Hepatic first pass effect;**
     - **Complete** ⇨ **Nitroglycerin** and **Lidocaine.**
     - **Partial** ⇨ **Propranolol** and **Morphine.**
     - **Minimal** ⇨ **Atenolol** and **Nadolol.**



- **To overcome hepatic first pass effect;**

  ☞ ***If partial*** ⇨ Increase the dose of the drug.

  ☞ ***If complete*** ⇨ Use another routes such as IV and sublingual.

****

➢ Factors Affecting Oral Absorption:-

1: Presence of food and other drugs in the GIT:

- **Amino acids** ⇨ ***compete*** for the ***same carrier*** of **L-dopa.**
- **Ca^{2+}** (*from* milk) ⇨ ***decrease*** **absorption** of **Tetracycline.**
- **Tannic acid** (*from* tea) or **Tetracycline** ⇨ ***decrease*** **absorption** of **Iron.**
- **Vitamin C** ⇨ ***enhances*** the **absorption** of **Iron.**
- **Food** ***dilutes*** *some* **drugs** ⇨ ***decrease*** **absorption** *this* **drugs.**

  ☞ **Food** is ***useful*** in **irritant drugs** ⇨ ***decrease*** **irritation.**

2: State of health of GIT:

- ***Presence*** of **disease** e.g. **Malabsorption syndrome** ⇨ ***decreases*** absorption.

3: Gastric emptying rate: ⇨ (process of emptying food from the stomach into the duodenum)

- May be ***increase*** or ***decrease*** **absorption** of the **drug** (***depend on the drug***):

  ☞ *For Example*: **1) Metoclopramide** ⇨ ↑ **emptying rate;**
  - ***Increase*** **absorption** of **Paracetamol** (***Rapid*** **rate** of **dissolution** and **disintegration**).
  - ***Decrease*** **absorption** of **Digoxin** (***Slow*** **rate** of **dissolution** and **disintegration**).

  2) Atropine ⇨ ↓ **emptying rate.**

4: GI Motility (Mobility):

- ***Increase*** **Motility** (Diarrhea) ⇨ ***decrease*** **absorption** of *some* **drugs.**
- ***Decrease*** **Motility** (Constipation) ⇨ ***Increase*** **absorption** of *some* **drugs.**

5: PH of GIT:

- ***Weak acid*** **drugs** (**Aspirin**) ⇨ **absorbed** in ***acidic*** **medium** (Stomach).
- ***Weak base*** **drugs** (**Ephedrine**) ⇨ **absorbed** in ***basic*** **medium** (Intestine).

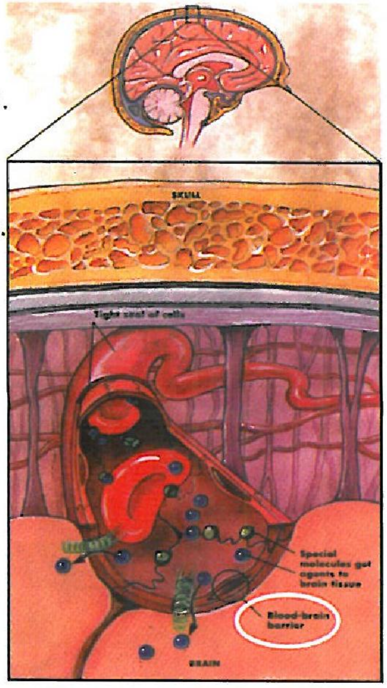
6: First pass effect: ⇨ ***Decrease*** **bioavailability.**

7: Related to the drug: (Lipid solubility).

- ***Lipid soluble*** **drugs** ⇨ ***Increase*** **absorption.**

(Like dissolve like)

- **Polar Drugs** (water soluble drug); are ***not*** *totally* **absorbed** (due to high amount of lipid content in the cells) and ***not*** **pass** *through* **Blood Brain Barrier (BBB).**
- **Non-polar Drugs** (lipid soluble drugs); are ***highly*** **absorbed** and *pass* **BBB.**



Blood-Brain Barrier (BBB)

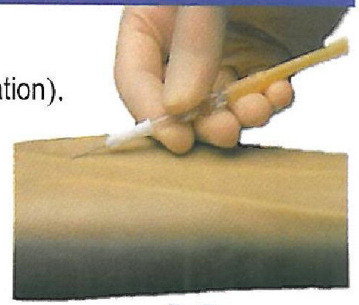
2: Parenteral Routes (injections):

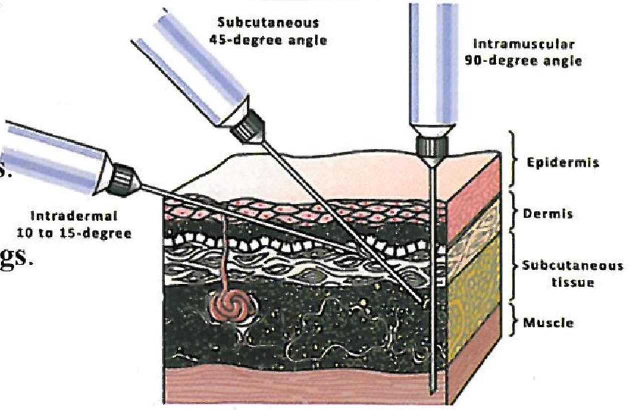
Drugs in parenteral routes must be sterile and free from pyrogen (fever inducing substance)

➢ A: Intravenous (IV) injection:

- *Slow* **bolus injection** or **infusion** (drip) *method*.
- *Used* **water solution** *only*.

- Advantage:
  - **100% bioavailability** (The % of drug reached to systemic circulation).
  - *Suitable for* **irritant drugs** and **large volume drugs**.
  - *Suitable for* **emergency**.
  - *Suitable for* **acid labile drugs**.
- Disadvantage:
  - *Low* **safety** (If allergy ⇨ Anaphylactic shock).
  - *Must be* **sterile** (Free from pyrogen).
  - *Spreading of* **infection** (Viral hepatitis).
  - *Required* **professional person**.
  - *Not suitable for* **oily** and **suspended drugs**.





➢ B: Intramuscular (IM) injection:-

- *Suitable for* **solution, suspension** and **oily drugs**.
- *Better* **absorption** *than* SC but *less than* IV.

➢ C: Subcutaneous (SC) injection:-

- **Absorption rate** is *slower than* **IV** and **IM**.
- It is *suitable for* **drugs** that are *non-irritant* in **aqueous solution** or **fine suspension**.

➢ D: Intradermal (ID) Injection:-

- **Sensitive tests** and **vaccination**.

Screenshot from Pulp Fiction (1994) movie

➢ E: Other injection:-

- E.g.;
  - **Intracardiac injection** ⇨ Adrenalin in cardiac arrest.
  - **Intra-bone marrow injection** ⇨ bone marrow cells injection.
  - **Intrathecal injection** ⇨ Spinal anaesthesia.
  - **Intraperitoneal (IP) injection** ⇨ peritoneal dialysis (PD).

3: Mucosal Route:

Buccal or Sublingual	Ocular	Vaginal	Nasal	Rectal
Systemic delivery of drugs	Local delivery of drugs	Systemic or local delivery of drugs		

4: Inhalation Route:

- *Systemic* **delivery** of **drugs**.
- *Highly* **blood supply** and *wide* **surface area**.
- *Highly* **absorbed** (high bioavailability).
- *Many* **drugs** may *cause* **lung irritants**.

5: Topical Route:

- **Topical application** is **used** *when* a **local effect** of the **drug** is *desired*.

6: Transdermal: (Transdermal Drug Delivery System - TDDS)

- This route of administration *achieves* **systemic effects** by *application* of **drugs** to the **skin**.
- This route is *most often* **used** for the *sustained delivery* of **drugs**, such as the **antianginal drug Nitroglycerin**, the *antiemetic* **Scopolamine** and **Nicotine transdermal patches**, which are *used to facilitate* **smoking cessation**.

IV > IM > SC > Oral > Skin

Dosage Forms

According to routes of administration

- Oral
  - Solid
    - **Powder** ⇨ Oral rehydration.
    - **Effervescent granules**
    - Tablets
      - **Simple tablet**
      - **Sugar coated tablet** ⇨ To mask bad taste.
      - **Enteric coated tablet** ⇨ Protects the drug from stomach acid.
      - **Extended-release tablets** ⇨ Sustained Release (SR) or Controlled Release (CR) or Timed Release (TR) or Retard.
        - have special coatings or ingredients that control the drug release.
    - Capsules
      - **Hard gelatin capsule** ⇨ Containing either powder or granules.
      - **Soft gelatin capsule** or **Softgel** ⇨ Containing liquid.
      - **Enteric coated capsule** ⇨ Protects the drug from stomach acid.
      - **Sustained release capsule** ⇨ Control the drug release.
  - Liquid
    - Aqueous
      - **Suspension** ⇨ Insoluble powder suspended in water. "Shake well before use"
      - **Syrup** ⇨ Sweet-flavoured preparation.
      - **Emulsion** ⇨ Fixed oil dispersed in water. "Shake well before use"
      - **Infusion** ⇨ by soak raw material in cold or hot water.
      - **Decoction** ⇨ by boiling raw material in water.
      - **Aromatic water** ⇨ Volatile oil in water.
    - Alcoholic
      - **Elixir** ⇨ Sweet-flavoured hydro alcoholic preparation.
      - **Spirit** ⇨ Volatile oil in alcohol.
      - **Tincture** ⇨ Alcoholic extract.
- Buccal
  - **Sublingual pellet** ⇨ Placement under the tongue ⇨ Systemic effect.
  - **Buccal spray** ⇨ Spray under the tongue.
  - **Lozenge** ⇨ Tablet dissolved slowly in mouth.
  - **Mouthwash (MW)** and **Mouth paint**
- Parenteral
  - **Subcutaneous Pellet Implantation** ⇨ Hormone pellet implantation.
  - **Ampoule** ⇨ Single use only.
  - **Vial** ⇨ Single or multiple use.
  - **Bottle** ⇨ Big container for IV infusion.
- Inhalation
  - **Inhaler or Puffer** ⇨ Metered-dose inhaler (MDI).
  - **Aerosol (Spray)** ⇨ Bottle that contains a liquid under pressure.
  - **Nebulizer** ⇨ Device convert liquid to a mist ⇨ more easily inhaled into the lungs.
  - **Spinhaler** ⇨ Crush a capsule with a medicine ⇨ inhaled finely micronized powder.
- Rectal
  - **Suppository** - **Enema.**
- Topical
  - Skin: **Ointment** - **Cream** - **Lotion** - **Collodion** - **Transdermal Delivery System**
  - Eye: **Eye Drops** - **Eye Ointment** - **Ocusert** e.g. Ocusert Pilocarpine system.
  - Ear: **Ear Drops** - **Ear Ointment**
  - Nose: **Drops** - **Spray** - **Inhaler**
  - Vagina: **Vaginal Tablets** - **Vaginal Ovule** - **Vaginal Douche** - **Vaginal Cream**

Pharmacokinetics

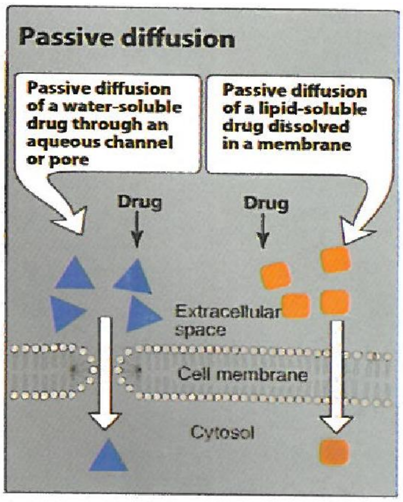
- **Def.** ⇨ *Effect of the* **body** *on the* **drug**.
- **Consist** *of* **4 process (ADME):-**

1- Absorption

- **Def.** ⇨ is the *transfer of* a **drug** *from* the **site** *of* **administration** to the **bloodstream**.
  - The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability).

- **Mechanisms of absorption of drugs from the GI tract:-**

1 Simple Diffusion (Passive diffusion):


Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
Extracellular space
Cell membrane
Cytosol

- The *majority* of **drugs** are **absorbed** *by this* **mechanism**.
- The **driving force** is the **concentration gradient**.
- *From* ***high*** **conc.** *to* ***low*** **conc.** (*along* **conc. gradient**).
- ***Not needed*** energy and **carrier**.
- ***Factors affecting simple diffusion***:-
  - **1: Dose concentration:**
    - ***Increase*** **dose concentration** ⇨ ***Increase*** **absorption**.
  - **2: Molecular weight & size:**
    - ***Increase*** **Mwt.** ⇨ ***Decrease*** **absorption**.
  - **3: Ionization:**
    - It **depends** ***upon*** **pH** of the **medium** and **pKa** of the **drug**.

{pKa ⇨ The negative logarithm of the dissociation constant or ionization constant (Ka)}.

Effect of pH on drug absorption

- **Most drugs are either *weak acids* or *weak bases*:**
- **Weak Acids:** Acidic drugs (HA) release a proton (H^+) and charged anion (A^-):

$$HA \leftrightarrow H^+ + A^-$$

- **Weak Bases:** Weak bases (BH^+) can also release an H^+.

$$BH^+ \leftrightarrow B + H^+$$

- A drug passes through lipid membrane more readily if it is uncharged (Unionized).
- ***Henderson-Hasselbalch equation*** for determination of degree of ionization:

- For weak acid drugs:

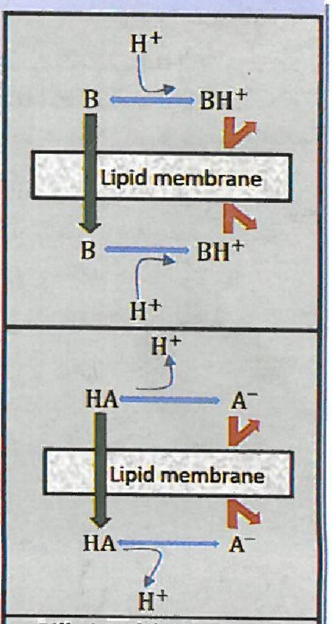
pKa = pH + log Unionized form / Ionized form

When pH is less than pKa ⇨ Unionized forms More Than Ionized forms.

- For weak base drugs:

pKa = pH + log ionized form / unionized form

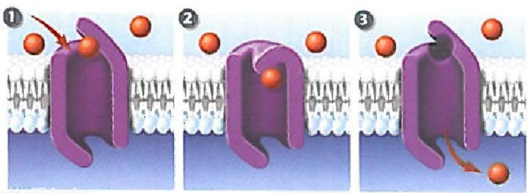
When pH is greater than pKa ⇨ Unionized forms More Than Ionized forms.


H+
B
BH+
Lipid membrane
B
BH+
H+
H+
HA
A−
Lipid membrane
HA
A−
H+

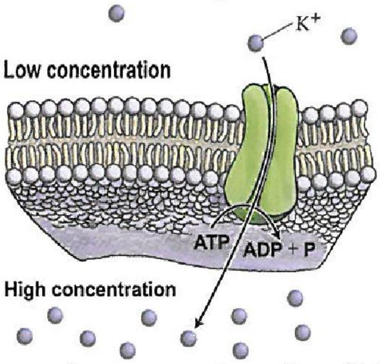
Diffusion of the non-ionized form of drugs through a lipid membrane.

Weak acid drugs ⇨ less ionized in *acidic* medium (Stomach) ⇨ *decrease* ionization ⇨ *Increase* Absorption.
Weak base drugs ⇨ less ionized in *basic* medium (Intestine) ⇨ *decrease* ionization ⇨ *Increase* Absorption.

2 Facilitate Diffusion:



- *From* ***high*** **concentration** to ***low*** **concentration.**
- ***Not need*** **energy.**
- ***Need*** **carrier proteins:**
  - ☞ Carrier proteins facilitate the passage of large molecules.
  - ☞ These carrier proteins undergo conformational changes, allowing the passage of drugs into the cell or endogenous molecules out the cell.
  - ☞ Facilitate Diffusion of some drugs may be inhibited by compounds that compete for the same carrier proteins.

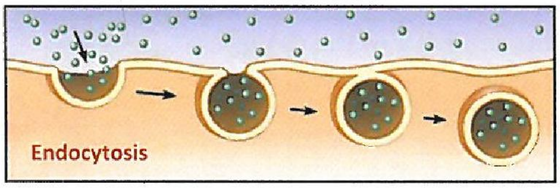


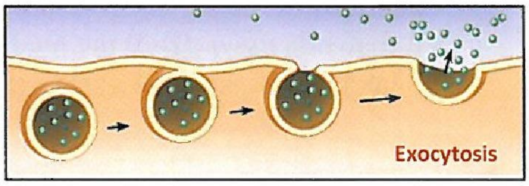
3 Active Transport:

- *From* ***low*** **conc.** to ***high*** **conc.** (***against*** **conc. gradient**).
- ***Need*** **specific carrier proteins.**
- ***Need*** **energy.**

4 Endocytosis (Pinocytosis) and Exocytosis:

- *This type* of absorption is *used to* ***transport*** **drugs** of ***exceptionally*** **large size** *across the* **cell membrane.**
- ***Endocytosis***: ***Engulfment*** of a **drug** *by the* **cell membrane** and ***transport*** *into the* **cell** *by* **pinching off** *the* **drug-filled vesicle.**
  - ☞ E.g. ⇨ *Transport of* **Vitamin B_{12}** ***across*** the **gut wall.**
- ***Exocytosis*** is the reverse of endocytosis.
  - ☞ E.g. ⇨ *Certain* **neurotransmitters** (e.g. **Norepinephrine**) are ***released by*** **exocytosis** *from* in **intracellular vesicles** in the **nerve terminal.**





➢ **Factors Affecting Absorption of Drugs:-**

1: Patient-Related Factors:

- **Routes of administration** ⇨ IV > IM > SC > Oral > Skin.
- ***Total*** **surface area** *available for* **absorption** ⇨ ***Increase*** **surface** ⇨ ***Increase*** **absorption.**
  - ☞ The intestine has a surface area about 1000-fold that of the stomach (containing microvilli).
- **Blood flow** to the **absorption site** ⇨ ***Increase*** **blood flow** ⇨ ***Increase*** **absorption.**
  - ☞ The intestines receive much more blood flow than the stomach.
- **Contact time** at the **absorption surface** ⇨ ***Increase*** **contact time** ⇨ ***Increase*** **absorption.**
- ***Presence*** of ***other*** **drugs** ⇨ **Ca^{2+}** (*from* milk) ⇨ ***decrease*** **absorption** of **tetracycline.**
- ***Expression*** of **P-glycoprotein** ⇨ ***Increase*** **expression** ⇨ ***decrease*** **absorption.**
  - ☞ P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes, it pumps drugs out of the cells.

2: Drug-Related Factors:

- **Lipid solubility** ⇨ ***High*** **lipid soluble drugs** ⇨ ***High*** **absorption.**
- **Ionization** ⇨ **Unionized drugs** ⇨ ***High*** **absorption.**
- **Valency** ⇨ **Ferrous iron** (Fe^{2+}) **absorbed** ***more than*** **ferric iron** (Fe^{3+}).
- **Nature** ⇨ **Inorganic** (Small molecules) > **Organic** (Big molecules).
- **Dosage forms** ⇨ **Solution > Suspension > Tablet**
- **pH** of the **medium** and **pKa** of the **drug** ⇨ *See previous page.*

2- Distribution

➢ **Def.** ⇨ ***Transfer*** of **drugs** *from* the **bloodstream** *into* the **interstitium** (extracellular fluid) and the **tissues.**

➢ **The distribution of a drugs depends on :-**

1 Blood Flow:

☞ ***Increase*** **blood flow** ⇨ ***Increase*** **distribution.**

- **Blood flow** to the "**vessel-rich organs**" (brain, liver and kidney) is ***greater than*** that to the **skeletal muscles, adipose tissue, skin** and **viscera.**
- *Example* ☞ **IV bolus** of **Propofol** (short duration hypnotic drug) ⇨ ***High*** **blood flow** & ***high*** **lipophilicity** of **Propofol** ⇨ ***Rapid distribution*** into the **CNS** ⇨ ***produces*** **anesthesia.**
  ⇨ ***Slower distribution*** into the **skeletal muscle** and **adipose tissue.**

Due to ***Rapid*** **distribution** ⇨ ***Decrease*** **plasma concentration** of **Propofol** ⇨ So that the **drug** ***diffuses*** ***out*** of the **CNS**, ***down*** the **concentration gradient** by ***passive diffusion*** ⇨ **Consciousness** is ***regained*** (***short duration***).

2 Capillary Permeability:

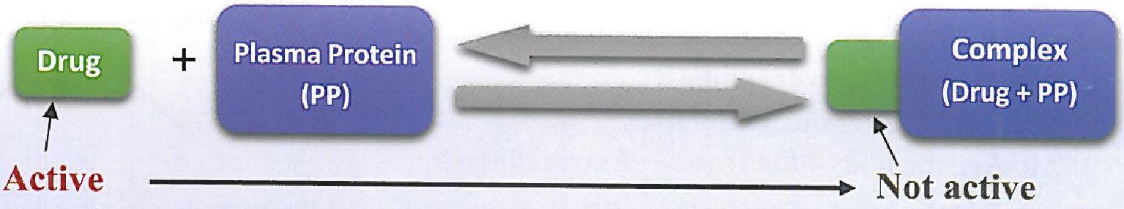
- It ***depends on*** **capillary structure** and the **chemical nature** of the **drug.**

☞ *In the* **liver** and **spleen** ⇨ ***Increase*** **capillary permeability** ⇨ **large plasma proteins** *can* **pass.**

☞ *In the* **brain** ⇨ ***only*** **lipid soluble drugs** *can* **pass** *through* **blood–brain barrier (BBB).**

3 Binding of Drugs to Plasma Proteins and Tissues:

A) Binding to Plasma Proteins



- **Albumin** is the ***major*** **drug-binding protein** and may ***act as*** a **drug reservoir.**
- ***Bound*** **fraction** of the **drug** ⇨ ***not active*** (not distributed, not metabolized and not excreted).
- ***Free*** **fraction** of the **drug** ⇨ ***active*** (distributed, metabolized and excreted).
- The **concentration** of ***free*** **drug** ***decreases*** due to **elimination** ⇨ the **bound drug** ***dissociates*** *from* the **protein** (to maintain equilibrium between free-drug and bound-drug).

- Factors affecting plasma protein binding:

1: Displacement of one drug by another drug:

☞ E.g. **Aspirin** and **Warfarin** (Anticoagulant) ⇨ **Aspirin** ***displaces*** **Warfarin** due to ***high*** **affinity** to **plasma proteins** ⇨ ***increase*** **free active Warfarin** ⇨ ***Increase*** **toxicity** of **Warfarin.**

☞ **Drugs** with ***high*** **affinity** to **plasma proteins** such as **Aspirin**, **Sulfonamides** and **Chloramphenicol** can ***replace*** the **other drugs** ***from*** the **binding site** in **plasma proteins** *such as* **Warfarin.**

2: Decrease in albumin or plasma proteins (liver diseases) ⇨ ***increase*** **free active drugs.**

B) Binding to Tissue Proteins

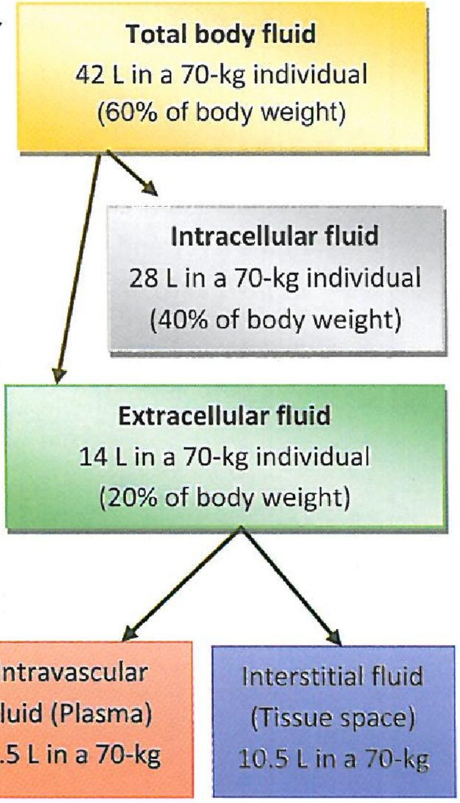
- ***Many*** **drugs** ***accumulate*** in **tissues**, ***leading to higher*** **concentrations** in **tissues** ***than*** in the **extracellular fluid** and **blood.**
- **Tissue reservoirs** may ***serve as*** a **major source** of the **drug** and ***prolong*** its **actions** or ***cause*** **local drug toxicity.**

4 Lipophilicity:

- **Lipophilic** ***(Non-polar)*** **drugs** ***readily*** **move** ***across most*** **biological membranes** ⇨ **these drugs** ***dissolve*** in the **lipid membranes** & ***penetrate*** the **entire cell surface** (depends on blood flow).
- **Hydrophilic** ***(Polar)*** **drugs** ***do not*** **readily** ***penetrate*** **cell membranes** and ***must*** **pass** *through* **slit junctions.**

5 Volume of Distribution (V_d):

- **Volume of distribution** (V_d), *also known as* **apparent volume of distribution.**
- ***Def.*** ⇨ **Fluid volume** that *would be* ***required*** *to* ***contain*** the ***amount*** of **drug** ***present*** *in the* **body** *at the* ***same*** **concentration** as in the **plasma.**
- V_d has ***no*** **physiologic** or **physical basis,** it can be ***useful*** to ***compare*** the **distribution** of a **drug** *with the* **volumes** *of the* **water compartments** *in the* **body.**


Total body fluid
42 L in a 70-kg individual
(60% of body weight)
Intracellular fluid
28 L in a 70-kg individual
(40% of body weight)
Extracellular fluid
14 L in a 70-kg individual
(20% of body weight)
Intravascular fluid (Plasma)
3.5 L in a 70-kg
Interstitial fluid (Tissue space)
10.5 L in a 70-kg

$$V_d = \frac{Q\ \text{(Total amount of drug in the body)}}{C_p\ \text{(Plasma concentration of the drug)}}$$

Patterns of distribution

1: Intravascular fluid (Plasma):

- **Drug** (High Mwt) is ***retained*** in the **blood compartment.**
- E.g. **Drug** ***pound*** to **plasma proteins** and **Heparin.**

2: Extracellular fluid (Intravascular + Interstitial):

- **Drug** (Small Mwt) ***can*** **filtrate** but ***cannot*** **pass** *through* **cell membrane (hydrophilic).**
- E.g. **Aminoglycoside antibiotics.**

3: All over the body fluid (Intra + Extracellular):

- **Drug** (small Mwt) ***can filtrate*** and ***can*** **pass** *through* **cell membrane (lipophilic).**

4: Tissue reservoirs:

Hair	Liver	Thyroid	Heart	Fats	Bone
Arsenic	Vitamin B_{12}	Iodine	Digitalis	Thiopentone	Ca^{2+}

5: Blood brain barrier (BBB): ⇨ Lipid cellular barrier ⇨ ***only*** **lipid soluble drugs** (Non-ionized).
⇨ **Inflammation** (Meningitis) ⇨ ***Increase*** **permeability** of **BBB.**

6: Placenta barriers: ⇨ Lipid cellular barrier.

- *If the* **drug** ***pass*** **placenta** *during* **pregnancy** ⇨ **Teratogenicity** e.g. **Tetracycline** & **Thalidomide**
- *If the* **drug** ***pass*** **placenta** *during* **labour** ⇨ **Neonatal asphyxia** e.g. **Morphine** & **barbiturates.**

- **Effect of V_d on drug half-life:**

- ***Increases*** V_d ⇨ ***increase*** the **half-life** and ***extend*** the **duration** of **action** of the **drug.**

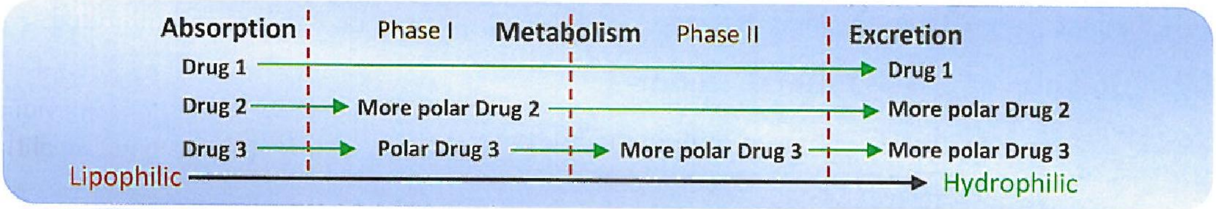
If the drug has ***high*** V_d ⇨ ***Low affinity*** to binding to plasma proteins
If the drug has ***low*** V_d ⇨ ***High affinity*** to binding to plasma proteins

- **Half-life** of a **drug** is ***directly proportional*** to the **volume of the distribution** and ***inversely proportional*** to the **clearance.**

3- Metabolism

- The **kidney** ***cannot*** *efficiently* ***eliminate*** **lipophilic** (non-polar) **drugs** that ***readily*** *cross* **cell membranes** and are ***reabsorbed*** in the **distal convoluted tubules**. *Therefore*, **lipid-soluble agents** are ***first*** **metabolized** *into* ***more*** **polar** (hydrophilic) **substances. Liver** is the ***main site*** of **drug metabolism.**
- **Drugs** can be ***metabolized by*** **oxidation, reduction, hydrolysis, hydration, conjugation, condensation**, or **isomerization.**

➢ **Def.** ⇨ ***Metabolism*** (***biotransformation***) *usually* ***conversion*** of **drug** *from* **non-polar (active)** ⇨ ***to*** **polar** (less active) ⇨ *to* ***more*** **polar** (not active) ⇨ *to* ***facilitate*** **excretion**.



Classification:-

Phase I

Phase I reactions ***convert*** **lipophilic drugs** ***into*** **more polar molecules** by ***introducing*** or ***unmasking*** **a polar functional group**, such as $-OH$ or $-NH_2$.

1: Oxidation e.g. **Phenacetin** ⇨ **Acetaminophen.**

2: Reduction e.g. **Chloral hydrate** ⇨**Tri-chloro ethanol.**

3: Hydrolysis e.g. **Acetylcholine** ⇨ **Choline** + **Acetic acid.**

Phase II
(Conjugation)

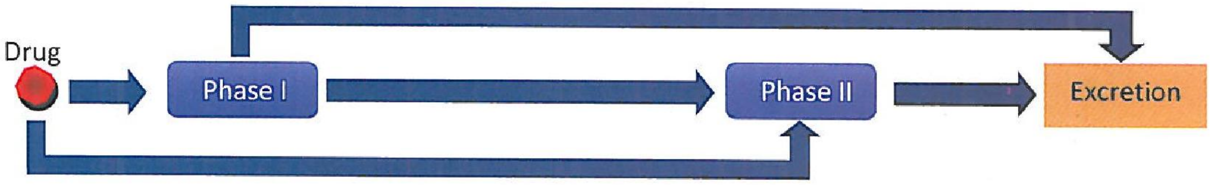
This phase consists of conjugation reactions.

Conjugation may be with ☞

1: Acetic acid (Acetylation) e.g. **Isoniazid**

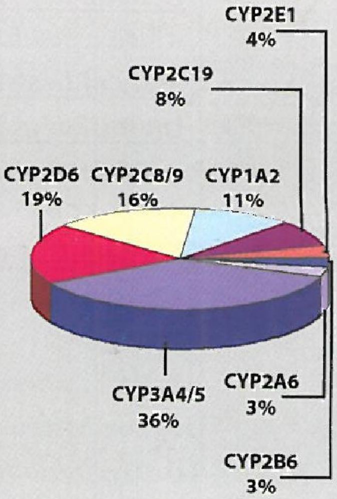
2: Methylation e.g. **Nor-adrenaline** ***3: Sulfate*** e.g. **Phenols**

4: Glycine e.g. **Aspirin** ***5: Glucuronic acid*** e.g. **Chloramphenicol**



Cytochrome P-450 (CYP450)

- The ***most important*** **enzyme system** of **phase I metabolism** is **CYP450**, that ***catalyses*** the **oxidation** of ***many*** **drugs.**
- **CYP**, is a **superfamily** of ***heme-containing isozymes*** that are ***located in*** **most cells**, ***but primarily*** in the **liver** and **GI tract.**
- ***Nomenclature***: The family name is *indicated by* the number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A. A second number indicates the specific isozyme, as in CYP3A4. The term P450 is derived from the spectrophotometric peak at the wavelength of the absorption maximum of the enzyme (450 nm).
- **CYP450 enzymes** can be ***induced*** or ***inhibited*** by ***many*** **drug.**
- *Because* there are ***many*** **different genes** that ***encode*** **multiple enzymes**, there are ***many*** **different P450** ***isoforms***.



Relative contribution of cytochrome P450 isoforms to drug biotransformation.

➢ Metabolism Enzymes:-

	Microsomal Enzymes	Non-Microsomal Enzymes
Majority	- *Majority* of drug biotransformation reaction.	- *Some* of drug biotransformation reaction.
Site	- **Smooth endoplasmic reticulum.**	- **Cytoplasm** and **mitochondria**.
Organs	- *Mainly* in **liver** *then* kidney, lungs, intestinal mucosa.	- **Hepatic cells** as well as in other tissues including plasma.
Phase I	- Catalyse oxidative (**CYP450**), reductive and hydrolytic reactions.	- Catalyse few oxidative, a no. of reductive and hydrolytic reactions.
Phase II	- Glucuronidation reactions ***only***.	- Also conjugation reaction ***other than*** glucuronidation.
Activity	- Can be induced and inhibited.	- ***Can't*** be induced and inhibited.

➢ Results of phase I metabolism:-

1	Acetylcholine **(Active)**	**Inactivation**	Choline + Acetic acid **(Inactive)**
2	Levodopa **(Inactive)**	**Activation**	Dopamine **(Active)**
3	Diazepam **(Active)**	**Maintain activity**	Nor-Diazepam **(Active)**
4	Methyl alcohol **(Non-toxic)**	**Toxification**	Formaldehyde **(Toxic-Blindness)**

➢ Factors Affecting Metabolism:-

- Age: ***Deficiency*** of **liver microsomal enzyme** ***especially in*** **child** ⇨ ***prolonged*** **action** of **drug** *lead to* ***increase*** **toxicity** e.g. **Chloramphenicol** when ***used*** in **babies** cause **Grey baby syndrome**.
- Sex differences: **Metabolic difference *between* sexes** have been noted for a number of drugs, this suggests that **hormonal activity** might *affect* the ***activity*** of ***certain*** **oxidation enzymes**.
- Genetic factors: ***Absence*** of **specific gene** *responsible for* **synthesis** of ***special*** **enzyme** which *essential for* ***normal*** **metabolism** (such as in **Favism**).
- State of health: ***Presence*** of **disease** (liver disease) ⇨ ***Alters*** in the **normal metabolism.**
- Inhibition of microsomal enzymes: *Certain* **drugs *inhibits*** the ***activity*** of **microsomal enzyme** ⇨ ***decrease*** **metabolism rate** ⇨ *leading to* ***prolongation*** the **action** of ***other*** **drugs** ⇨ ***increase*** **activity** and may *leading to* **toxicity** of ***other*** **drugs.**
- Induction of microsomal enzymes: *Certain* **drugs *increase*** the **activity** of **microsomal enzyme** ⇨ *leading to* ***increase*** **metabolism rate** ⇨ ***decrease*** **activity** of ***other*** **drugs.**

Hepatic Microsomal Enzyme (HME) ***inducers*** (examples)	**Carbamazepine**, **Phenytoin**, **Phenobarbital** and **Rifampicin.**
Hepatic Microsomal Enzyme (HME) ***inhibitors*** (examples)	**Cimetidine**, **Chloramphenicol**, **Omeprazole**, **Erythromycin** and **Ketoconazole.**

4- Excretion

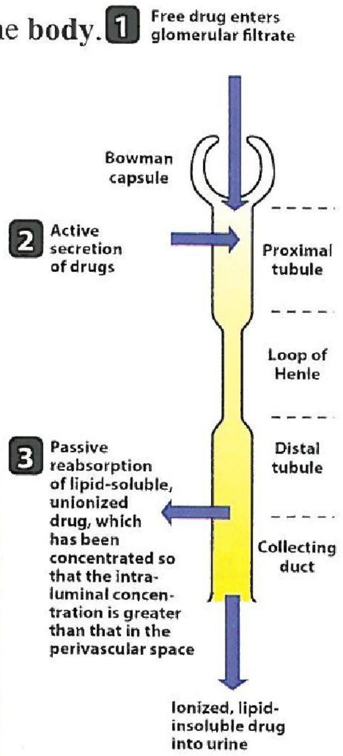
- **Def.** ⇨ The **process** which *involve* **excretion** of **drug** *outside* of the **body.**
- **Routes of drug excretion (elimination):**

Kidney	GIT	Skin	Lung
	- **Saliva** Morphine - **Bile** ⇨ **Feces** into the intestinal tract.	***Sweat gland*** Rifampicin ***Breast (milk)*** Nicotine Morphine	Anesthetic Gases e.g. Nitrous oxide & Halothane

1: Glomerular filtration: For water soluble non bound drugs (Most).
2: Proximal (Active) tubular secretion: e.g. Penicillin.
3: Distal (Passive) tubular reabsorption: For lipid soluble drugs.

- ***Reabsorption may affected by pH :-***

- *Acidification* of urine (Vit. C) ⇨ *Increase* excretion of *basic drugs.*
- *Alkalization* of urine ($NaHCO_3$) ⇨ *Increase* excretion of *acidic drugs.*


1 Free drug enters glomerular filtrate
Bowman capsule
2 Active secretion of drugs
Proximal tubule
Loop of Henle
Distal tubule
3 Passive reabsorption of lipid-soluble, unionized drug, which has been concentrated so that the intraluminal concentration is greater than that in the perivascular space
Collecting duct
Ionized, lipid-insoluble drug into urine

Method used to Prolong Duration of Action of Drugs

1 Decrease Absorption

1) Add Vasoconstrictor
(Adrenaline + local anesthesia)
2) Use sparingly soluble complex
(Protamine zinc insulin)
3) Use of drug in oil
(Vasopressin in oil)
4) Use of slow release (SR) tablets
5) Use SC pellet implantation
(DOCA in Addison's disease and contraception)

2 Decrease Metabolism

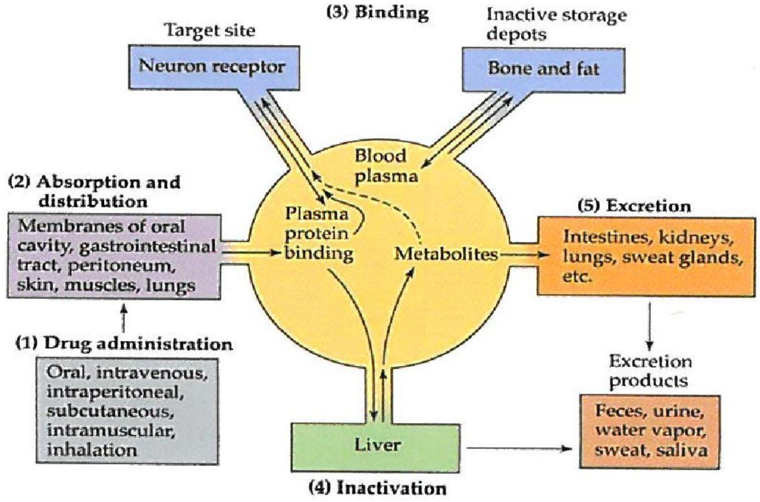
Use HME inhibitors e.g.
Omeprazole & Erythromycin

3 Decrease Excretion

Probenecid with Penicillin

4 Increase protein binding

Add methoxy group to sulfonamide

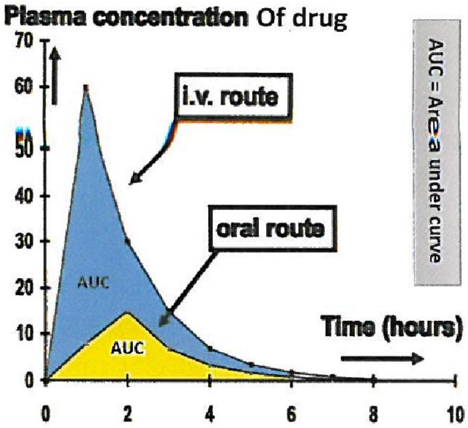

Target site
Neuron receptor
(3) Binding
Inactive storage depots
Bone and fat
(2) Absorption and distribution
Membranes of oral cavity, gastrointestinal tract, peritoneum, skin, muscles, lungs
Blood plasma
Plasma protein binding
Metabolites
(5) Excretion
Intestines, kidneys, lungs, sweat glands, etc.
(1) Drug administration
Oral, intravenous, intraperitoneal, subcutaneous, intramuscular, inhalation
Excretion products
Feces, urine, water vapor, sweat, saliva
Liver
(4) Inactivation

Pharmacokinetic Parameters

1) Bioavailability (BA)

➢ **Def.** ⇨ is the **fraction** (%) of an ***administered* dose** that is **absorbed** *from its* **site** of **administration** and *reaches* (in an ***unchanged* form**) the **systemic circulation**.

Oral bioavailability (F) = $AUC_{oral}/AUC_{iv} \times 100$



➢ **Factors affecting bioavailability:-**

- **First pass effect** ⇨ ***Decrease*** **bioavailability**.
- **Physicochemical properties** of the **drug**.
  (Polarity – Solubility – Particle size)
- **Nature** of ***formulation***.
  (Solution > Suspension > Tablet)

➢ **N.B:**

- **Bioequivalence:**
  - **Two drug formulations** are ***bioequivalent***; *if* they ***show*** **comparable bioavailability** and ***similar*** **times** *to* **achieve** ***peak*** **blood concentrations**.
- **Therapeutic Equivalence:**
  - **Two drug formulations** are ***therapeutically equivalent***; *if* they are **pharmaceutically equivalent** (same dosage form, contain the same active ingredient, and use the same route of administration) with ***similar*** **clinical** and **safety profiles**.

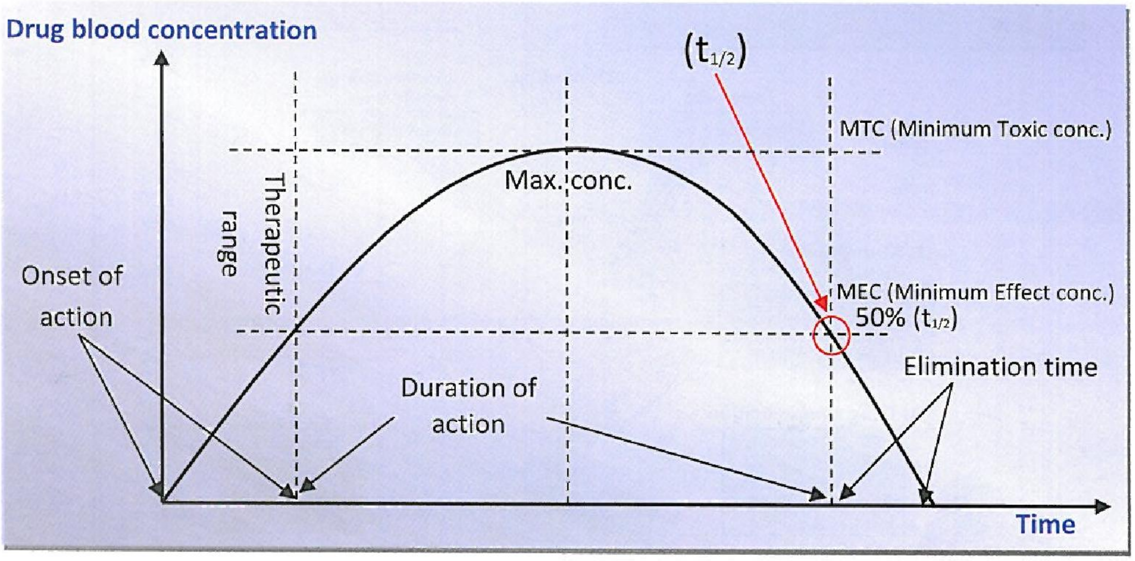
2) Volume of distribution (V_d)

- *See page no.* (10).

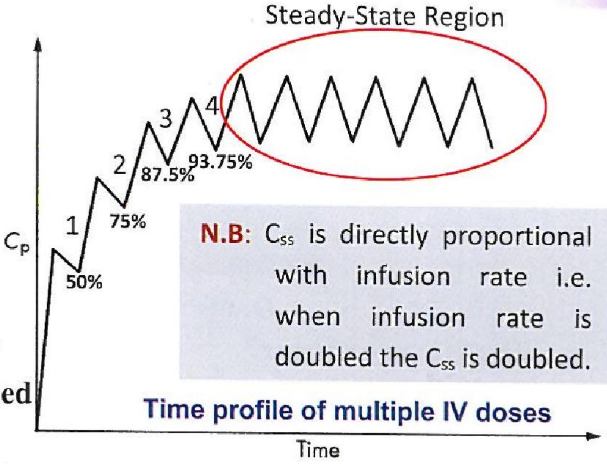
3) Plasma half-life ($t_{1/2}$)

➢ **Def.** ⇨ **Time** *needed by the* **body** to *decrease* a **plasma concentration** of **drug** *to its* **half**.
⇨ **Time** it *takes* for the **amount** of **drug** in the **body** to be ***reduced by*** **50%**.

- The **half-life** of a **drug** ***depends on*** its **clearance** and **volume** of **distribution**.
- **Half-life** ***determines*** the ***length*** of the **drug effect**.
- ***According to plasma level-time curve:***


Drug blood concentration
(t1/2)
MTC (Minimum Toxic conc.)
Max. conc.
Therapeutic range
Onset of action
MEC (Minimum Effect conc.)
50% (t1/2)
Elimination time
Duration of action
Time

- **Multiple doses:**
  - *Some* **drugs** *may be* **used** ***clinically*** on a **single-dose basis**, *although most* **drugs** are ***administered*** **continually** ***over*** a **period** *of* **time**.
  - When a **drug** is ***administered*** at a **regular dosing interval** (orally or IV), the **drug** ***accumulates*** in the **body** and the **serum concentration** will **rise** ***until steady-state conditions*** have been **reached**



N.B: C_{ss} is directly proportional with infusion rate i.e. when infusion rate is doubled the C_{ss} is doubled.

Time profile of multiple IV doses

- **Steady-State Concentration (C_{ss}):**
  - **Steady state** ***occurs*** when the **amount** of **drug** ***administered*** is **equal** to the ***amount*** of **drug eliminated** in that ***same*** **period**. - ***Time required to reach the C_{ss}:***
    - After First $t_{1/2}$ ⇨ Drug concentration = 50%, Second $t_{1/2}$ ⇨ Drug concentration = 75%, Third $t_{1/2}$ ⇨ Drug concentration = 87.5%, Fourth $t_{1/2}$ ⇨ Drug concentration = 93.75%

Loading dose = $V_d \times C_{ss}$

☞ **Drug reaches steady state in about four to five half-lives.**

4) Clearance (Cl)

➢ **Def.⇨** **Volume** of **plasma** *which* **drug** is ***completely*** **cleared** ***per*** **unit time** (ml/min).

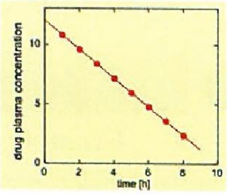
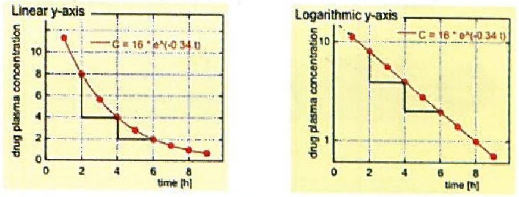
$$Cl_{Organ} = Q \text{ (blood flow in organ) } X \text{ ER (Extraction Ration)}$$

$$ER = (C_A - C_V)/C_A$$

C_A (drug entering the organ arterial side) - C_V (drug leaving the organ venous side)

$$Cl_{total} = Cl_{Hepatic} + Cl_{Renal} + Cl_{Pulmonary} + Cl_{others}$$

5) Elimination Kinetics

		Zero-Order Elimination	First-Order elimination
Def.		- **Elimination** *of the* **drug** which is ***independently*** of the **drug conc.** - *For example*: **1.2 mg** are ***eliminated every*** **hour**.	- **Elimination** *of the* **drug** which is ***dependently*** of the **drug conc.** - *For example*: ***increase*** **drug conc.** *lead to* ***increase*** **rate** of **drug elimination**.
Elimination rate		- **Elimination rate** ***saturates*** with ***higher*** **drug concentration**.	- **Elimination rate** is ***proportional*** *to* **drug concentration**.
Curve			
	C vs t	**Linear**	**Exponential decay**
	Log C vs t	**Non-linear**	**Linear**
Term		**Non-linear** (Saturation)	**Linear**
Example		- A ***few substances*** are **eliminated** by **zero-order elimination kinetics**, *because* their **elimination process** is ***saturated***. Examples are **Ethanol**, **Phenytoin**, **Salicylates**, and **Omeprazole**.	- **95%** of the **drugs** in **use** ***at*** **therapeutic concentrations** are **eliminated** *by* **first order elimination kinetics**.

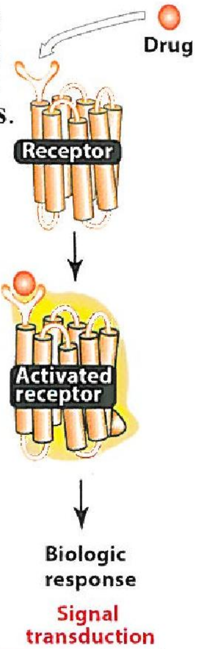
Pharmacodynamics

- **Def.** ⇨ Is the **effect** *of the* **drug** *on the* **body** (Mechanism of action).
  - *Most* **drugs** ***exert*** *their* **effects** (beneficial or harmful) by ***interacting*** *with* **receptors**.
  - **Drug** ***interact*** with **receptor** to form **drug–receptor complex**.

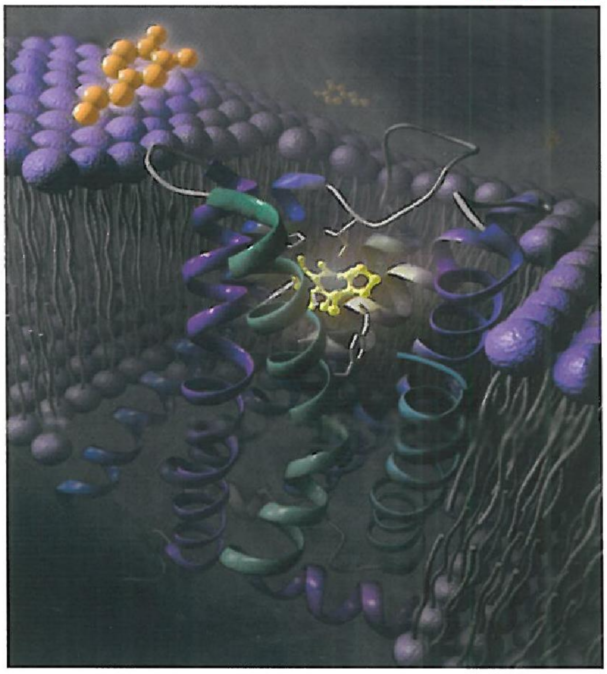
Drug-Receptor Interactions

Drug + Receptor = Drug-Receptor complex

- **What is a receptor?**
  - *Any* **biological molecule** to *which* a **drug** ***binds*** and ***produces*** **response**.
  - **Drug** or ***any*** **substance** (***activate*** or ***inactivate*** **receptor**) *called* ⇨ **Ligand**.
  - **Drug–receptor complex** *initiates* ***alterations*** in **biochemical** and/or **molecular** ***activity*** of a **cell** by a **process** *called* **signal transduction**.
  - **Drugs** *act as* **signals**, and ***their*** **receptors** act as **signal** ***detectors***.
  - **Second messenger** or **effector molecules** are ***part*** of the ***cascade*** of **events** that ***translates*** **agonist** ***binding*** *into* a **cellular** ***response***.


Drug
Receptor
Activated receptor
Biologic response
Signal transduction

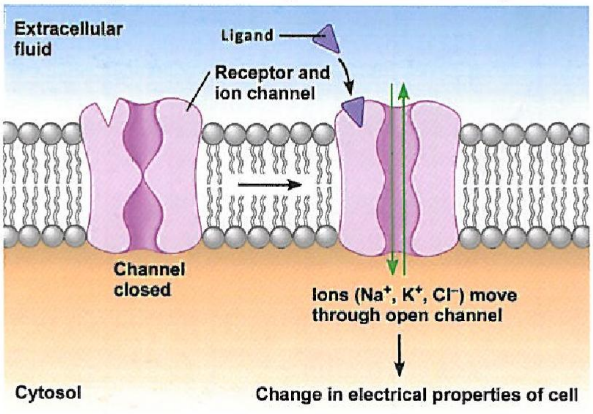
- **Major classes of receptors:-**
  1) **Ligand-gated Ion Channels**.
  2) **G Protein-Coupled Receptors** (**GPCRs**).
  3) **Intracellular Receptors**.
  4) **Enzyme Linked Receptors**.



Dopamine 3 Receptor (GPCR) structure in pdb (Protein Data Bank) format

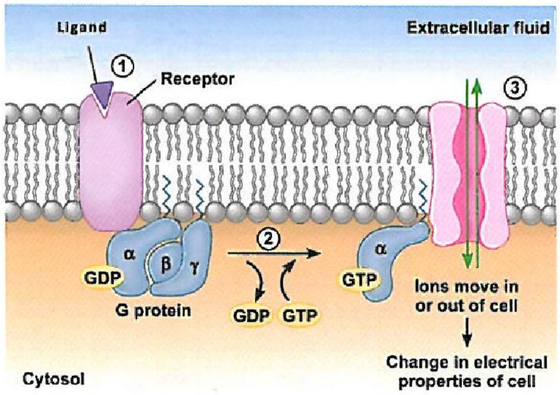
1 Ligand-gated ion channels

Example: Cholinergic nicotinic receptors


Extracellular fluid
Ligand
Receptor and ion channel
Channel closed
Ions (Na$^+$, K$^+$, Cl$^-$) move through open channel
Change in electrical properties of cell
Cytosol

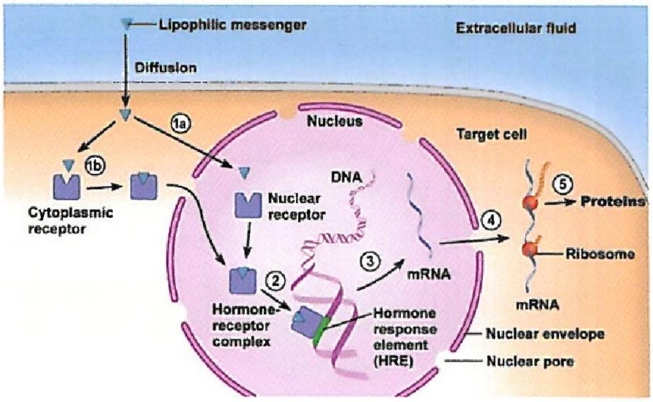
2 G Protein-Coupled Receptors (GPCRs)

Example: α and β adrenoceptors


Ligand
①
Receptor
Extracellular fluid
③
α
β
γ
GDP
G protein
②
GDP
GTP
GTP
α
Ions move in or out of cell
Change in electrical properties of cell
Cytosol

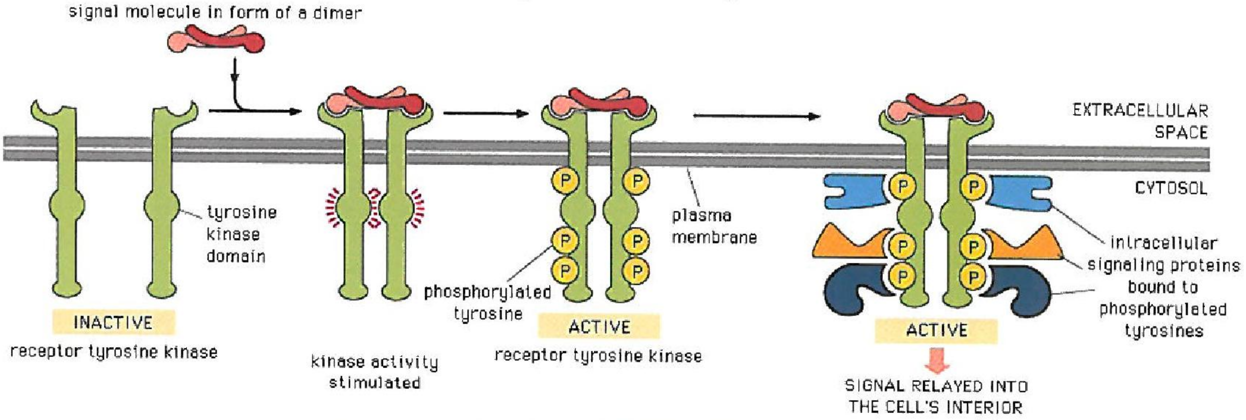
3 Intracellular receptors

Example: Steroid receptors

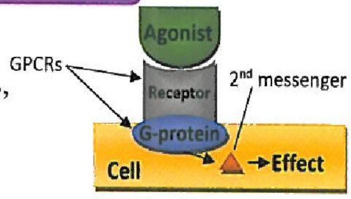

Lipophilic messenger
Extracellular fluid
Diffusion
1a
Nucleus
Target cell
1b
Cytoplasmic receptor
Nuclear receptor
DNA
⑤
Proteins
④
Ribosome
③
mRNA
②
Hormone-receptor complex
Hormone response element (HRE)
mRNA
Nuclear envelope
Nuclear pore

4 Enzyme linked receptors (Tyrosine kinase linked receptor)

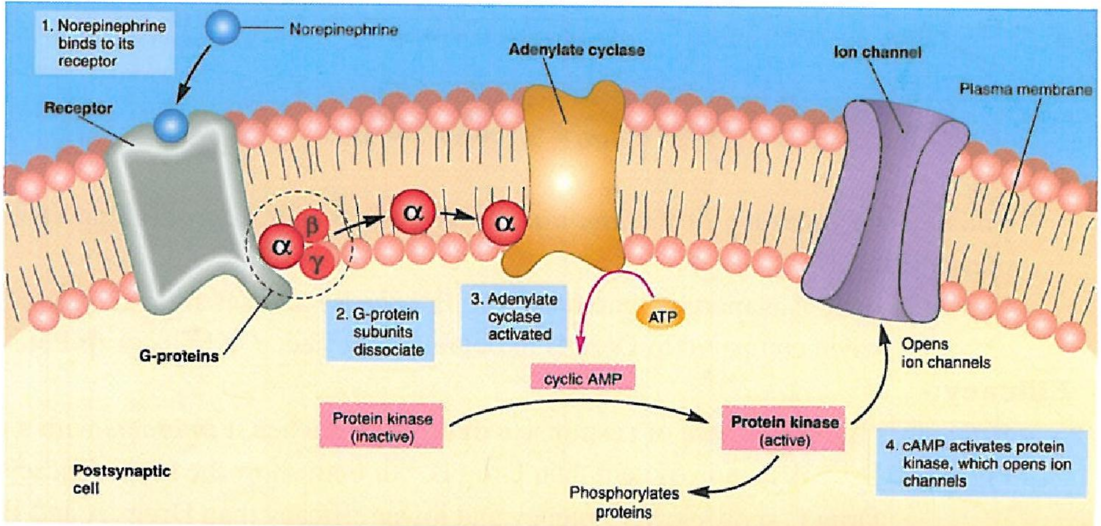
Example: Insulin receptors.


signal molecule in form of a dimer
tyrosine kinase domain
INACTIVE
receptor tyrosine kinase
kinase activity stimulated
P
phosphorylated tyrosine
ACTIVE
receptor tyrosine kinase
plasma membrane
EXTRACELLULAR SPACE
CYTOSOL
intracellular signaling proteins bound to phosphorylated tyrosines
ACTIVE
SIGNAL RELAYED INTO THE CELL'S INTERIOR

G Protein–Coupled Receptors (GPCRs)

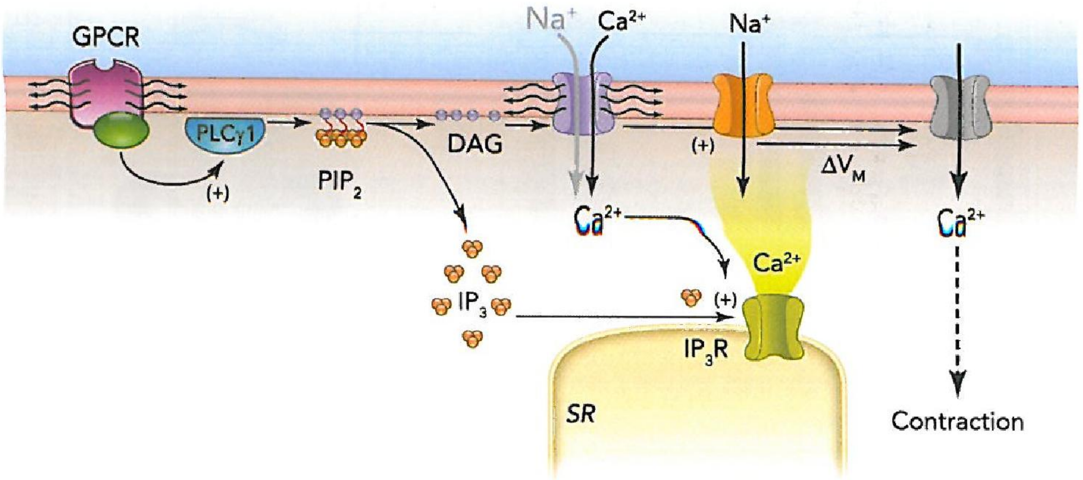

Agonist
GPCRs
Receptor
2nd messenger
G-protein
Cell
Effect

- **G Protein–Coupled Receptors (GPCRs):**
  - ***Also known as*** ⇨ seven-transmembrane domain (7TM) receptors, heptahelical receptors, serpentine receptor and G protein–linked receptors (GPLR).
  - ***Def.*** ⇨ are integral membrane proteins with seven membrane spanning helices ⇨ upon binding to a ligand ⇨ activate second messenger ⇨ alter in cell activity.
  - ***Structure*** ⇨ The extracellular domain of this receptor contains the ligand-binding area, and the intracellular domain interacts (when activated) with a G protein or effector molecule.
- **Second messenger system:**
  - ***Def.*** ⇨ are intracellular signalling molecules released by the cell to trigger physiological changes (one of intracellular signal transduction cascades).
  - ***Examples*** ⇨Cyclic AMP, Cyclic GMP, Inositol Triphosphate, Diacylglycerol, and Calcium.
- **Main types of GPCRs:**
  - ***There are many kinds of G proteins*** for example, G_s, G_i and G_q.
    - **G_s (Stimulatory)** ⇨ ***Activate*** adenylate cyclase ⇨ ***Increase*** cyclic adenosine monophosphate (cAMP) ⇨ ***open*** Ca^{2+} channels and ***Increase*** Ca^{2+} influx from sarcoplasmic reticulum (SR) ⇨ ***Contraction***. ***Example*** ⇨ **β_1 and β_2 adrenoceptors**.
    - **G_i (Inhibitory)** ⇨ ***Inhibits*** adenylate cyclase ⇨ ***Decrease*** cAMP ⇨ ***Decrease*** Ca^{2+} ⇨ Inhibition. ***Example*** ⇨ **α_2 adrenoceptors**.


1. Norepinephrine binds to its receptor
Norepinephrine
Receptor
Adenylate cyclase
Ion channel
Plasma membrane
α
β
γ
α
α
G-proteins
2. G-protein subunits dissociate
3. Adenylate cyclase activated
ATP
cyclic AMP
Opens ion channels
Protein kinase (inactive)
Protein kinase (active)
4. cAMP activates protein kinase, which opens ion channels
Postsynaptic cell
Phosphorylates proteins

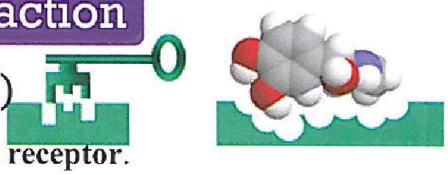
- **G_q (Stimulatory)** ⇨ ***Activate*** phospholipase-C (PLC) ⇨ PLC break phosphatidylinositol bisphosphate (PIP_2) into Inositol triphosphate (IP_3) and Diacylglycerol (DAG) ⇨ IP_3 ***increase*** Ca^{2+} influx from sarcoplasmic reticulum (SR) ⇨ ***Contraction***.

Example ⇨ **α_1 adrenoceptors.**



Ligand-Receptor Interaction

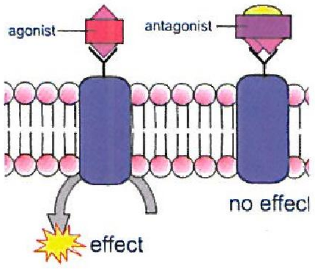
(Lock & key Theory)



- **What is a Ligand?** ***Any* substance** can ***interact** with* a **receptor**.
- **Types of Ligand:-**

Ligand has affinity and activate the receptor ➡ ***Agonist***

Ligand has affinity and not activate the receptor ➡ ***Antagonist***



Dose Response Curve

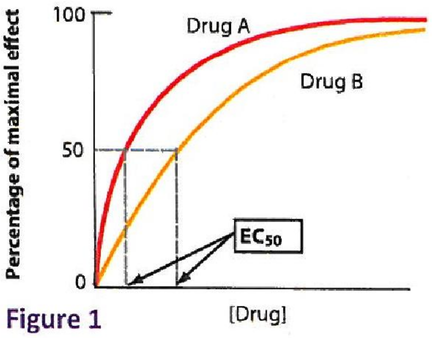


Figure 1

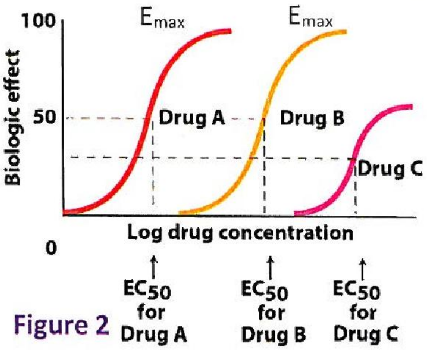
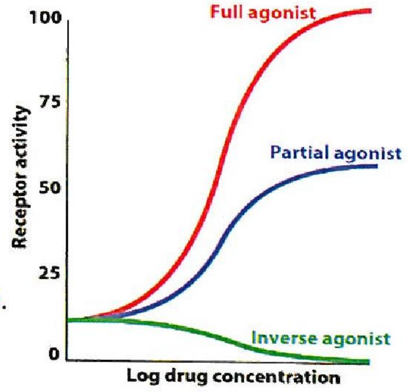


Figure 2

- **E_{max}:** maximal effect that produced by lowest dose of drug.
- **EC_{50}:** The conc. of drug producing 50% of the maximum effect. Usually used to determine potency.

- **Potency:-**
  - ***Potency*** is a **measure** of the ***amount*** of **drug necessary** to ***produce*** an **effect** of a ***given*** **magnitude.**
  - **Figure 1**: Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50% effect. (↓ EC_{50} ⇨ ↑ Potency).
- **Efficacy:-**
  - ***Efficacy*** is the ***magnitude*** of **response** a **drug *causes*** when it ***interacts*** with a **receptor**.
  - **Figure 2**: Drug A is more potent than Drug B, but both show the same efficacy. Drug C shows lower potency and lower efficacy than Drugs A and B.

Types of Agonists



Full Agonist

- If a **drug** ***binds*** to a **receptor** and ***produces*** a ***maximal response*** that ***mimics*** the **response** to the ***endogenous*** **ligand**.
- *Example*: **Phenylephrine** is a ***full*** **agonist** at **α_1-adrenoceptors**, *because* it ***produces*** the ***same*** E_{max} as does the ***endogenous*** **ligand**, **Norepinephrine**.

Partial Agonist

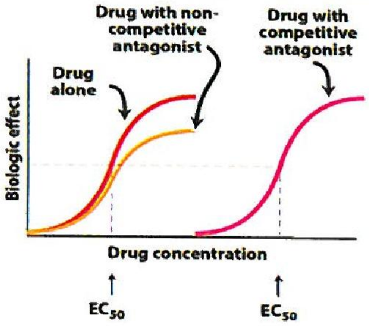
- Produces a ***partial*** **response** that ***mimics*** the **response** to the ***endogenous*** **ligand**.
- *Example*: **Aripiprazole**, an antipsychotic drug, is a ***partial*** **agonist** at **dopamine** ***receptors***.
- **N.B** ☞ Partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. When a receptor is exposed to both a partial agonist and a full agonist, the partial agonist may act as an antagonist of the full agonist.

Inverse Agonist

- ***Produce*** a **response** ***below*** the **baseline response** ***measured*** in the ***absence*** of **drug**.
- ***Decreases*** the **number** of ***activated*** **receptors**.

- ***N.B***; **Spare receptors**; in some receptor systems e.g. acetylcholine at the neuromuscular junction in smooth muscle, agonists are able to elicit maximal response at very low levels of receptor occupancy (<1%). Thus the system has spare receptors or receptor reserve. This arrangement produces an economy of neurotransmitter production and release.

Types of Antagonists (Blockers)

<table>
<tr><th>Competitive</th><th colspan="2">Non-competitive</th></tr>
<tr><td>- Competed with the agonist on receptor and displaced by increase the dose of agonist.</td><td colspan="2">- Act on the different site on the receptor and not displaced by increase the dose of agonist.</td></tr>
<tr><td>- Parallel shift to the right in the curve.</td><td colspan="2">- Non-Parallel shift to the right in the curve.</td></tr>
<tr><td>- Decrease potency ⇨ Increase EC_{50}.</td><td colspan="2">- Same potency ⇨ Same EC_{50}.</td></tr>
<tr><td>- Same efficacy ⇨ Same E_{max}.</td><td colspan="2">- Decrease efficacy ⇨ Decrease E_{max}.</td></tr>
<tr><td>- E.g. Atropine in muscarinic Ach receptors.</td><th>Reversible</th><th>Irreversible</th></tr>
<tr><td rowspan="3">
 </td><td>- Bind reversibly</td><td>- Bind irreversibly</td></tr>
<tr><td>- Short acting</td><td>- Long acting</td></tr>
<tr><td>- E.g.; Succinylcholine</td><td>- E.g.; Phenoxybenzamine</td></tr>
</table>

Regulation of Receptors

- ***Continuous*** **stimulation** *of* **receptors** *with* **agonists** ⇨ ***Decrease*** **number** of **receptors** and ***decrease*** **sensitivity** ⇨ ***down regulation***.
- ***Continuous*** **blocking** *of* **receptors** *with* **antagonists** ⇨ ***Increase*** **number** of **receptors** and ***increase*** **sensitivity** ⇨ ***up regulation***.

Dose

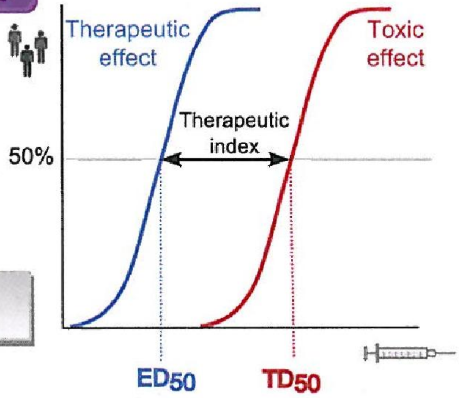
- **Def.** ⇨ A **quantity** of **medicine** ***prescribed*** *to be* **taken** at **one** ***time***.
- **Types of Doses:-**
  - **Therapeutic dose:** The ***average*** **dose** that ***produce*** **therapeutic effect.**
  - **Maximum tolerated dose:** The ***largest*** **dose** of a **drug** that *can be* **taken** ***safely***.
  - **Initial dose:** The **dose** ***used*** *at start of* **treatment**.
  - **Maintenance dose:** The **dose** *required to* ***maintain*** the **therapeutic effect**.
  - **Lethal dose or fetal dose:** The **dose** that ***produce*** **death**.

Therapeutic Index (TI)

- **Therapeutic index** = ***Measure*** of **drug safety**.
- ***Def.*** ⇨ is the ***ratio*** of the **dose** that ***produces*** **toxicity** in ***half*** the **population** (**TD_{50}**) *to the* **dose** that ***produces*** a **clinically desired** or **effective response** (**ED_{50}**) in ***half*** the **population**.

$$TI = \frac{LD_{50}}{ED_{50}}$$

↑ TI ⇨ ↑ Drug safety



N.B: ***Quantal dose response curve*** are useful for determining doses to which most of the population responds.

Standard Margin of Safety (SMS)

- ***Def.*** ⇨ The ***ration*** of the **dosage** ***required*** *to* **kill 1%** of **population** *compared to* the **dosage** that is ***effective*** in **99%** of **population**.
- The ***higher*** **margin** of **safety** ⇨ the ***better*** and **safer**.

$$SMS = \frac{LD_1}{ED_{99}}$$

- **Factors affecting the dosage and action of the drugs :-**

1: Age, weight and body surface area:

- ***Adult*** (20 - 60 years of age) **dose** and **weight** *about* **70 kg.**
- **Elderly** *required* ***small*** **dose** (due to ***decrease*** **renal excretion** and ***decrease*** **hepatic metabolism**).
- **Children** *required* ***small*** **dose** (due to ***immature*** **kidney** and **liver** and ***decrease*** **plasma protein**).
- ***Calculation*** of **child** and **infant dose** *from* **adult dose**.

❖ **Young's formula :**

$$\text{Child dose} = \frac{\text{Adult dose X Age in years}}{(\text{Age} + 12)}$$

❖ **Dilling's formula :**

$$\text{Child dose} = \frac{\text{Adult dose X Age in years}}{20}$$

❖ **Clark's formula :**

$$\text{Infant dose} = \frac{\text{Adult dose X Wt. in pounds}}{150}$$

2: Sex:

- *Some* **drugs** **female** *need smaller* **dose** *than* **male** due to ☞
  - ❖ *High* **fat content** ⇨ *Increase* **fate** in the **body** ⇨ *slow rate* of **oxidation** ⇨ *decrease* **metabolism** ⇨ *Increase* **drug effect.**
  - ❖ *Effect of* **sex hormone** (**Estrogen**) on **liver Microsomal enzyme** (LME) (*inhibitors*).
  - ❖ *Some* **drug** ***avoided*** *during* **pregnancy** and **lactation**.

3: Routes of Administration:

- IV > IM > SC > Oral

4: Time of Administration:

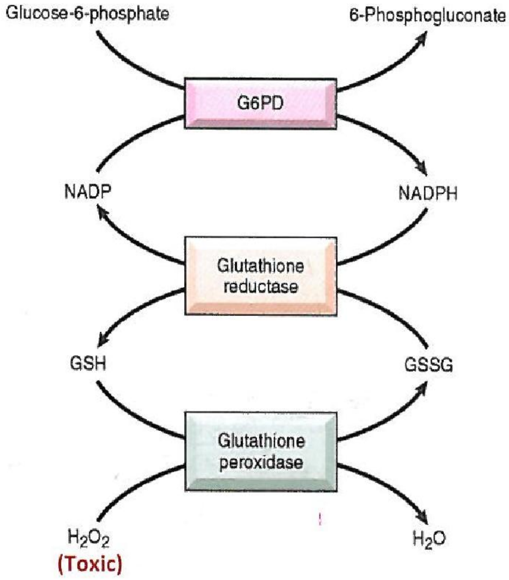
- **Irritant drugs** are **better** *taken after* **meals** e.g. **Aspirin**.
- **CNS** (Central Nervous System) ***stimulant*** **drugs** ***should be not*** **given** at ***night*** they *may* **cause insomnia** e.g. **Ephedrine**.

5: Genetic Abnormality (Drug Idiosyncrasy)

- **Idiosyncrasy** (**Pharmacogenetics**) ⇨ ***Abnormal*** **reaction** *due to* **genetic** ***abnormality***.

  Example ☞

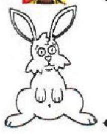
  - **Primaquine**, **Sulfa** and **chloramphenicol** are drugs may *induce* **hemolytic anemia** (hemolysis of RBCs) in **patient** *with* **glucose-6-phosphate dehydrogenase** ***(G6PD)*** **enzyme** ***deficiency***.
  - **G6PD enzyme** ***protects*** **RBCs** *from* **damage**.
  - **G6PD enzyme** ***responsible for*** *convert* **NADP** *into* **NADPH** *which* **make** ***detoxification*** of the **drugs** *through* **glutathione system**.



6: Hypersusceptibility (Supersensitivity) (Drug Intolerance)	7: Hypersensitivity (Drug Allergy)
- The **greater response** to **Adrenaline** in **thyrotoxic patient.** - **Drug intolerance** is ***commonly*** **observed** in **infant** ⇨ *because* **metabolism** and **excretion** ***not*** **fully** ***developed***.	- **Antibody-antigen interaction** ⇨ ***increase*** **release** of **Histamine**. ☞ ***Symptoms*** (**Anaphylaxis** or **Anaphylactic shock**) - ***skin reaction*** (e.g.: skin rash & oedema) - ***Fever*** - ***Asthmatic attack*** (difficulty in breathing) - E.g. in **patients** ***sensitive to*** **Penicillin**.

8: Tolerance:

- **Def.** ⇨ ***Failure*** of **responsiveness** to the ***usual*** **dose**.
- **Types of Tolerance:**
  - ✓ **Congenital Tolerance:**



    - ❖ **Racial** ⇨ **Ephedrine** is ***not*** **mydriatic** in **Negroes**.
    - ❖ **Species** ⇨ **Rabbits** is *tolerated* **large amount** of **belladonna** *due to* ***atropine esterase enzyme*** in **rabbit liver** and **plasma** which ***rapidly detoxification*** of **atropine**.
    - ❖ **Individual** ⇨ **Genetic factors** are *possibly* **involved**.

✓ Acquired Tolerance:

- *Increase the* **dose** *to* **obtain** *the* **original** *effect*.
  - ❖ **Cross-Tolerance** e.g. **antianxiety drugs** and **sedative hypnotics**.
  - ❖ **Tachyphylaxis** (acute or sudden) ⇨ e.g. **Ephedrine** ⇨ **Sudden** *increase* **blood Pressure** then *decrease* (gradually).
  - ❖ **Bacterial resistance to antibiotics.**

Mechanism of acquired tolerance (Drug desensitization)

Receptor Mediated	Non-Receptor Mediated
(Down-regulation of receptor) - *Loss* of receptor ***function***. - ***Reduction*** of **receptor** ***numbers***.	- ***Physiological*** **adaptation**. - ***Reduction*** of **receptor-coupled signalling component**. - ***Reduction*** of **drug** ***concentration***. - ***Change*** in **kinetics** of **drugs**.

Drug Dependence

- It **usually** ***occurs*** with **CNS acting drugs**.
- It is a **phenomena** *related to* **tolerance**.
- It ***involves*** a *certain* **degree** of **tissue adaptation**.
- ***Withdrawal*** of the **drug** could *produce* **certain** ***unpleasant*** **symptoms**.

Habituation	Addiction
- ***Mild*** **degree** of **drug dependence**. - ***Psychic*** **dependence**. - *When* **drug** ***stopped*** ⇨ develop some **emotional distress** for a ***relative*** **short period**. - E.g. **Smoking** and **Coffee**.	- ***More serious*** **form** of **drug dependence**. - ***Psychic*** and ***physical*** **dependence**. - *When* **drug** ***stopped*** ⇨ ***Withdrawal symptoms*** ⇨ reverse the normal pharmacological action. - E.g. **Morphine** and **Heroin**.

Drug Interactions

After drug administration

A Pharmacokinetic Interactions

1) Absorption

- ***Gastric emptying rate:-***
  - **Atropine** ***decrease*** **absorption** of **Paracetamol** due to ***decrease*** **gastric emptying rate**.
- ***pH of the site of absorption:-***
  - **Weak acid drugs** *more* **absorbed** in the **stomach** and **weak base drugs** *more* **absorbed** in **intestine**.
- ***Presence of food and other drugs in the GIT.***

2) Distribution

- **Aspirin** ***displace*** **oral anticoagulants** and **oral hypoglycemic** from their **plasma binding** ***sites*** ⇨ ***increase*** **activity** of **anticoagulants** and **oral hypoglycemic drugs**.

3) Metabolism

- ***HME inducers*** e.g. **Phenytoin** ⇨ ***increase*** **metabolism** of **drugs metabolized** by **HME**.
- ***HME inhibitors*** e.g. **Cimetidine** ⇨ ***decrease*** **metabolism** of **drugs metabolized** by **HME**.

4) Excretion

- **Probenecid** ⇨ ***decrease*** **excretion** of **Penicillin**.
- **pH change** e.g. **acidification of urine** ⇨ ***Increase*** **excretion** of **weak base drugs**.

B Pharmacodynamic Interactions

Drug interact *with* ***another*** **drug** when ***presence*** of **both** in the **body**

If increase in drug effects

Addition (Summation)

- ***Algebraic sum*** of the **2 drugs** ***effect***.
- 1 + 1 = 2
- E.g. **Acetylcholine** + **Histamine** in ***contraction*** of **intestine**.

Synergism

- The **combination effect** ***more than*** **algebraic sum.**
- 1 + 1 = > 2
- E.g. **Ethanol** and **Barbiturates** → ***Severe*** ↓ **CNS**.

Potentiation

- **Drug** which ***increase*** the **effect** of ***other*** **drug**.
- 0 + 1 = > 1
- E.g. **Physostigmine** + **Acetylcholine**

If decrease in drug effects

Antagonism

Chemical Antagonism

- **Chemical interaction** *between* **2 drugs** → ***decrease*** **absorption**.
- E.g. **Heparin** + **Protamine sulfate**

Physiological (Functional) Antagonism

- **2 drugs** act on **2** ***different*** **receptors** → ***different*** **mechanism of action** → ***different*** **effect**.
- E.g. **Adrenaline** and **Histamine**

Adrenaline ⇨ Bronchi ⇨ β_2 ⇨ ***Bronchodilatation***.
Histamine ⇨ Bronchi ⇨ H_1 ⇨ ***Bronchoconstriction***.

Pharmacological Antagonism

- **2 drugs** act on the ***same*** **receptor** but ***one*** of ***them*** is ***agonist*** and the ***other*** is ***antagonist***.

Non-competitive
Organophosphate with **Acetylcholine**

Competitive
Atropine with **Acetylcholine**

Add Your Updates or Notes

Revision and Questions with Answers

Autonomic Nervous System (ANS)

(AUTONOMIC NERVOUS SYSTEM)

Subject — No. of page

Sympathetic and Parasympathetic 25
Neurotransmitters 28
Autonomic Receptors 30
Effect of Stimulation of Sympathetic and Parasympathetic 32

Drugs Affecting the Autonomic Nervous System

Cholinergic (Parasympathetic) Drugs

Cholinoceptor Agonists

Muscarinic Agonists 36
Nicotinic Agonists 42

Cholinoceptor Antagonists

- Muscarinic Antagonists 43
- Nicotinic Antagonists 49
  - Ganglion Blockers (GB) 49
  - Neuromuscular Blockers (NMB) 50

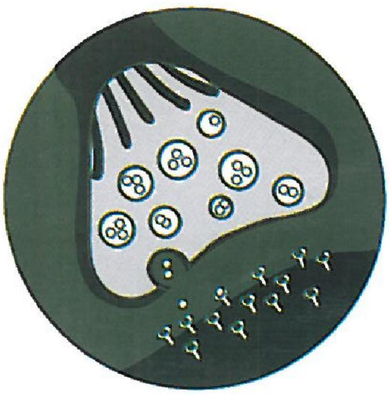
Adrenergic (Sympathetic) Drugs

Adrenoceptor Agonists

Direct-acting Adrenergic Agonists 56
Indirect-acting Adrenergic Agonists 68
Mixed-acting Adrenergic Agonists 71

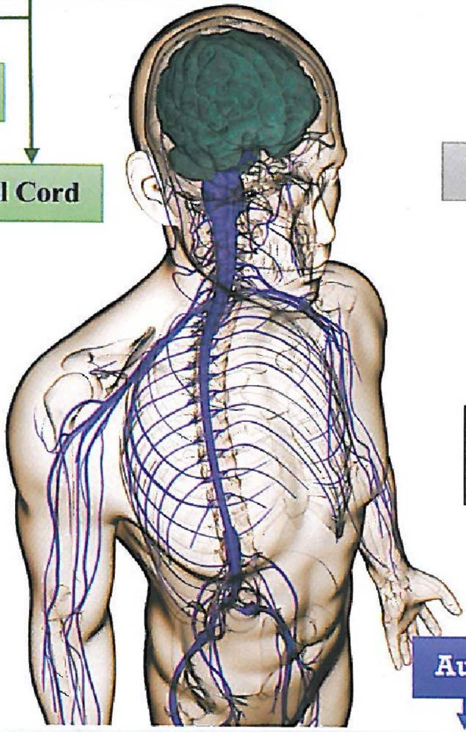
Adrenoceptor Antagonists

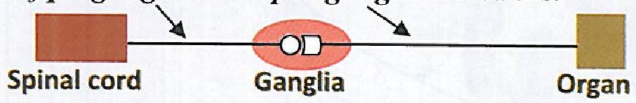
α-adrenoceptor Antagonists 73
β-adrenoceptor Antagonists 79
Adrenergic Neuron Blockers 84



Nervous System

- **Central Nervous System (CNS)**
  - **Brain**
  - **Spinal Cord**
- **Peripheral Nervous System (PNS)**
  - Outside the brain and spinal cord
    - **Efferent Division**
      - Carry signals away from the brain and spinal cord to the peripheral tissues
        - **Somatic Nervous System**
        - **Autonomic Nervous System**
    - **Afferent Division**
      - Bring information from the periphery to the CNS. Important in the reflex regulation of the system). For example, by sensing pressure in the carotid sinus and aortic arch).



Autonomic Nervous System	Somatic Nervous System
- ***Supply*** **cardiac muscle, smooth muscle** and **exocrine gland**.	- ***Supply*** **skeletal muscle**.
- ***Relay*** in **autonomic ganglia** (relay station) which *consist of* ***preganglionic*** & ***postganglionic*** **fibers**. 	- ***Don't relay*** *in* **ganglia**.
- ***Involuntary*** ⇨ ***under*** *the* **control** of **CNS**.	- ***Voluntary***.

1) Sympathetic

(Thoraco-Lumbar outflow)

☞ **Preganglionic neurons** *arise from* **thoracic** and **lumbar regions (L1 to L2)** of the **spinal cord**.

- *Consist of* ***short*** **preganglionic fibers** and ***long*** **postganglionic fibers**.

Chemical Transmitters

- **Adrenaline** and **Noradrenaline**.

⇨ **Except**: ***Thermoregulatory*** (eccrine) **sweat gland** and **adrenal medulla** they ***release*** **Ach** (**Acetylcholine**)

2) Parasympathetic

(Cranio-Sacral outflow)

☞ **Preganglionic neurons** *arise from* **cranial nerves** **3rd** (Oculomotor) **7th** (Facial) **9th** (Glossopharyngeal) **10th** (Vagus) and from **2nd**, **3rd** and **4th sacral segments**.

- *Consist of* ***long*** **preganglionic fibers** and ***short*** **postganglionic fibers**.

Chemical Transmitters

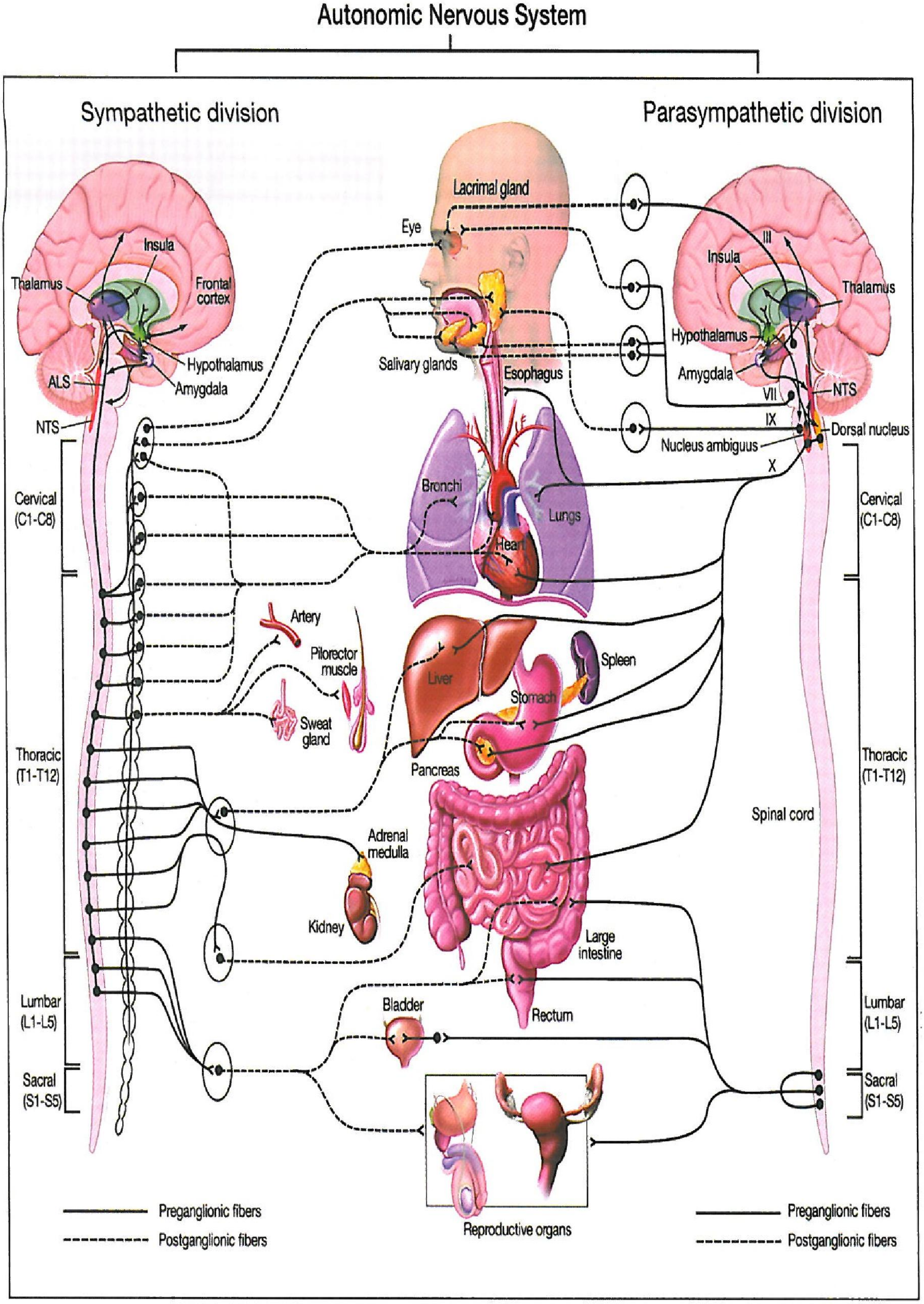
- **ACh** (**Acetylcholine**).

3) Enteric neurons

- It is a ***collection*** of **nerve fibers** that ***innervate*** the **GIT**, **pancreas**, and **gallbladder**, and it ***constitutes*** the "**brain** *of* **the gut**".
- This **system functions** ***independently*** of the **CNS** and ***control*** the **motility**, **exocrine** and **endocrine** ***secretions***.
- It is ***modulated*** by ***both*** the **sympathetic** and **parasympathetic nervous system**.

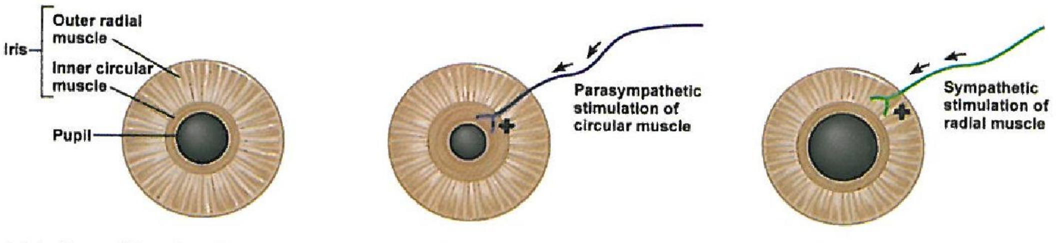
➢ Most Organs in the Body are Innervated by Both Divisions of the ANS:

(Dual Innervation)


Autonomic Nervous System
Sympathetic division
Parasympathetic division
Thalamus
Insula
Frontal cortex
Hypothalamus
Amygdala
ALS
NTS
Cervical (C1-C8)
Thoracic (T1-T12)
Lumbar (L1-L5)
Sacral (S1-S5)
Lacrimal gland
Eye
Salivary glands
Esophagus
Bronchi
Lungs
Heart
Artery
Pilorector muscle
Sweat gland
Liver
Spleen
Stomach
Pancreas
Adrenal medulla
Kidney
Large intestine
Rectum
Bladder
Reproductive organs
Insula
Thalamus
Hypothalamus
Amygdala
III
VII
IX
X
NTS
Dorsal nucleus
Nucleus ambiguus
Cervical (C1-C8)
Thoracic (T1-T12)
Spinal cord
Lumbar (L1-L5)
Sacral (S1-S5)
Preganglionic fibers
Postganglionic fibers
Preganglionic fibers
Postganglionic fibers

➢ Some Organs are Supplied with One Division of ANS:

- **Iris sphincter (pupillary constrictor) muscle** (*Circular*) ⇨ ***Supplied** by* **parasympathetic** (M_3).
- **Iris dilator (pupillary dilator) muscle** (***Radial***) ⇨ ***Supplied** by* **sympathetic** (α_1).


Iris
Outer radial muscle
Inner circular muscle
Pupil
Parasympathetic stimulation of circular muscle
Sympathetic stimulation of radial muscle
+
+

(a) Anatomy of iris and pupil (b) Pupillary constriction (c) Pupillary dilation

- **Arrector pili muscle** (**pilomotor muscle**) ⇨ ***Supplied** by* **sympathetic** (α_1) ⇨ **hair erection.** The ***contraction*** of the **muscle** is therefore **involuntary–stresses** e.g. **cold, fear** (**Goosebumps**).
- **Thermoregulatory** (**Eccrine**) **sweat gland** ⇨ ***Supplied** __only__ by* **sympathetic fibers, __but__** *through* **cholinergic (parasympathetic) receptors** (M_3).
- **Adrenal medulla** ⇨ ***Supplied** __only__ by* **sympathetic fibers, __but__** *through* **nicotinic (parasympathetic) receptors** (N_N).
- **Ventricles of the heart and Kidney** ⇨ ***Supplied** by* **__both__ innervations *__but__ only*** **sympathetic** are ***active*** (β_1); role of the parasympathetic innervation is still unclear.
- **Blood Vessels** ⇨ **Vascular smooth muscle** is ***innervated*** *__primarily__* by the **sympathetic** and *__indirectly__* ***non-innervated*** by the **parasympathetic**.

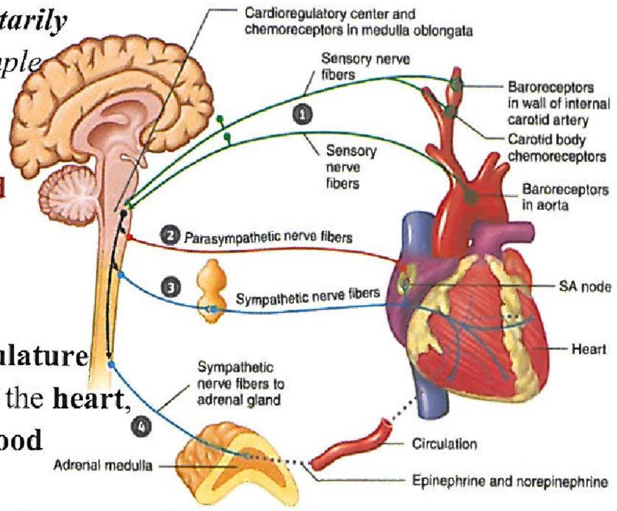
  I.e. ☞ ***Direct*** **acting** ⇨ ***innervated*** **__sympathetic__** ⇨ **α_1 receptors (Vasoconstriction).**

  ☞ ***Indirect*** **acting** ⇨ ***Non-innervated*** **__parasympathetic__** ⇨ **M_3 receptors (Vasodilatation)** via the **nitric oxide (NO)/endothelium *derived* relaxing factor** (no direct innervation).

➢ Role of the CNS in the Control of Autonomic Function:

- **ANS** is *provided by **streams*** of **afferent impulses,** ***originating*** in the **viscera** and ***other*** **autonomically innervated structures** that ***travel*** to **integrating centers** in the **CNS**, such as the **hypothalamus, medulla oblongata** and **spinal cord**. These **centers *respond to*** the **stimuli** by ***sending out*** **efferent reflex impulses** *via* the **ANS**.

1) **__Reflex arc__**: **A reflex arc** is a **neural *pathway*** that ***controls*** an **action reflex.** ***Most*** of the **afferent impulses** are ***involuntarily*** *translated into* **reflex responses.** *For example* a ***fall*** in **blood pressure** causes ***pressure*-sensitive neurons** (**__baroreceptors__** in the **heart, vena cava, aortic arch,** and **carotid sinuses**) to ***send fewer*** **impulses** to **cardiovascular centers** in the **brain.** This ***prompts*** a **reflex response** of ***increased*** **sympathetic *output*** to the **heart** and **vasculature** and ***decreased*** **parasympathetic *output*** to the **heart,** which ***results*** in a ***compensatory*** **rise** in **blood pressure** and **tachycardia.**

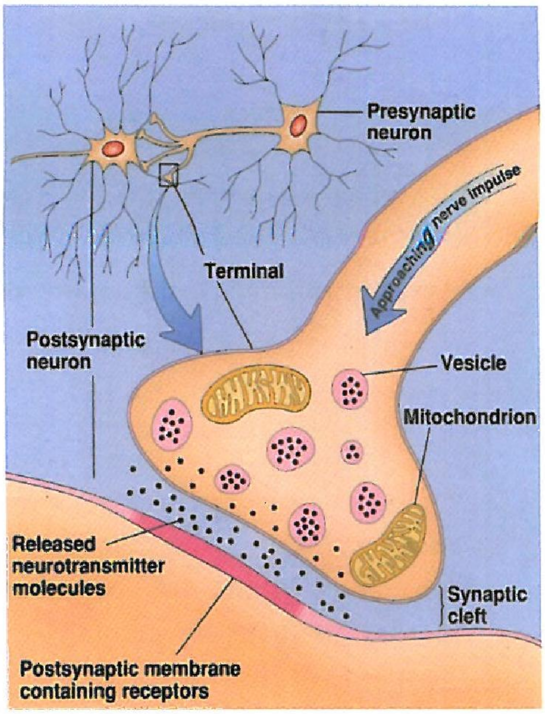

Cardioregulatory center and chemoreceptors in medulla oblongata
Sensory nerve fibers
①
Sensory nerve fibers
Baroreceptors in wall of internal carotid artery
Carotid body chemoreceptors
Baroreceptors in aorta
② Parasympathetic nerve fibers
③
Sympathetic nerve fibers
SA node
Heart
Sympathetic nerve fibers to adrenal gland
④
Circulation
Adrenal medulla
Epinephrine and norepinephrine

2) **__Emotions__**: ***Stimuli*** that *evoke **strong*** **feelings**, such as **rage, fear,** and **pleasure**, can ***modify*** the **activities** of the **ANS.**

Neurotransmitters

- **Def.** ⇨ **Neurotransmitters** or **Chemical transmitters** are ***endogenous*** **chemicals** that ***transmit*** **signals** ***across*** **a synapse** ***from*** **one neuron** (nerve cell) ***to*** **another** 'target' **neuron**.

History:


Presynaptic neuron
Approaching nerve impulse
Terminal
Postsynaptic neuron
Vesicle
Mitochondrion
Released neurotransmitter molecules
Synaptic cleft
Postsynaptic membrane containing receptors

Synapse

- Until the early 20th century, scientists assumed that the majority of synaptic communication in the brain was electrical.
- However, through the careful histological examinations by Ramón y Cajal (1852–1934), a 20 to 40 nm gap between neurons, known today as the ***synaptic cleft***, was discovered.
- The presence of such a gap suggested communication via chemical messengers traversing the synaptic cleft.
- Neurotransmission in the ANS is an example of the more general process of chemical signaling between cells.
- In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators.

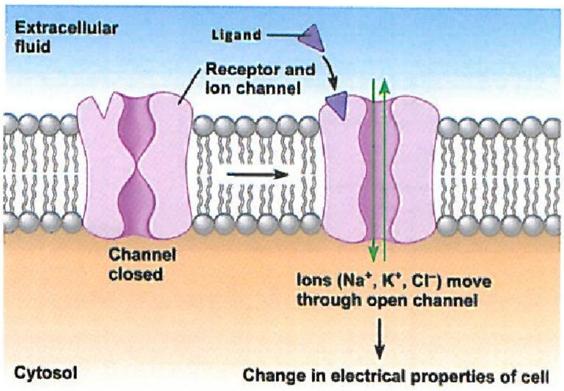
Chemical Transmitters in the ANS:

- **Chemical transmitter** *for* **parasympathetic**; **Acetylcholine (ACh)**.
- **Chemical transmitter** *for* **sympathetic** is ***mainly***; **Adrenaline** and **Noradrenaline**.
- **Chemical transmitter** *for* **sympathetic** and **parasympathetic** **ganglia**; **Acetylcholine**.
- ***Other transmitters involved:*** *called* ☞ **Non-Adrenergic Non-Cholinergic (NANC) transmitters**.
- ***Some of the NANC found in peripheral nervous system:***

Non-Adrenergic Non-Cholinergic (NANC) Transmitters	
Substance	**Probable Roles**
Nitric Oxide (NO)	- Act as Co-transmitter in non-innervated parasympathetic in blood vessels which responsible for vasodilator effect such as in penis erection.
Adenosine triphosphate (ATP)	- Act as Co-transmitter at many ANS-effector synapses.
Serotonin (5-HT)	- Act as Co-transmitter in ENS (Enteric Nervous System).
Dopamine	- Act as Co-transmitter in ENS. - Found in postganglionic sympathetic transmitter in renal blood vessels.
Calcitonin gene-related peptide (CGRP) and Substance-P	- Found in cardiovascular sensory nerve fibers. - Act as sensory neuron transmitter in ENS. - Vasodilator effect (probably via NO release).
Gamma-Amino-Butyric Acid (GABA)	- Has some relaxant effect on gut. - Not major transmitter in ENS.
Neuropeptide Y (NPY)	- Found in sympathetic neurons, cause long-lasting vasoconstriction.
Vasoactive Intestinal Peptide (VIP)	- Act as Co-transmitter in many parasympathetic neurons. - Vasodilator effect.

➢ Signal Transduction in the Effector Cell:

- The ***binding*** of **chemical substance** (**neurotransmitter**) *to* **receptors** ***activates*** **enzymatic processes** ***within*** the **cell membrane** that *ultimately* **results** in a **cellular response**.
- ***Activation*** of **cell** *through* **phosphorylation** of ***intracellular*** **proteins** or ***changes*** in the ***conductivity*** of **ion channels**.
- **Neurotransmitter receptors** are **membrane proteins** that ***provide*** a **binding site** that ***recognizes*** and ***responds*** to **neurotransmitter molecules**.
- **Neurotransmitter receptors** *such as:* (full text see pages 16, 17 & 18).
  - **Receptors coupled to ion channels (Ionotropic Receptors):**
    - Some receptors, such as the postsynaptic nicotinic receptors in the skeletal muscle cells, are directly linked to membrane ion channels.
    - Therefore, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability.


Extracellular fluid
Ligand
Receptor and ion channel
Channel closed
Ions (Na^+, K^+, Cl^-) move through open channel
Cytosol
Change in electrical properties of cell

  - **Receptors coupled to G-Protein (Metabotropic Receptors):**

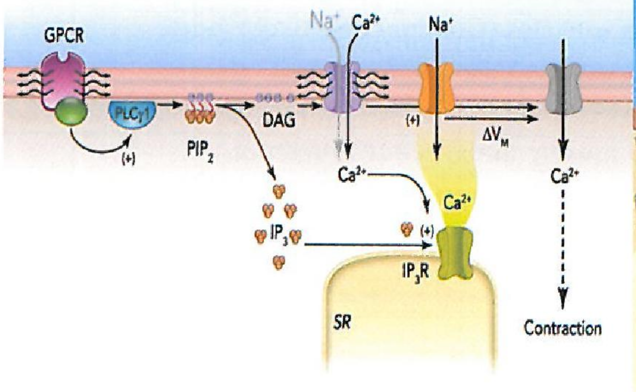
☞ Acts through a secondary messengers.

- ***There are many kinds of G proteins*** for example, G_s, G_i and G_q.

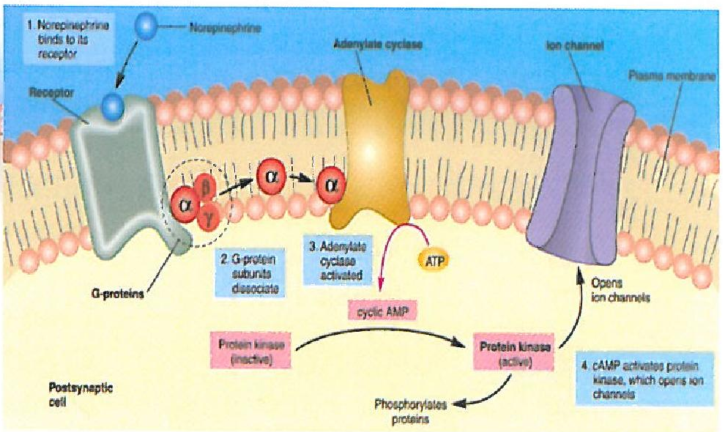
☞ **G_s (Stimulatory)** ⇨ ***Activate*** adenylate cyclase ⇨ ***Increase*** cyclic adenosine monophosphate (cAMP) ⇨ ***open*** Ca^{2+} channels and ***Increase*** Ca^{2+} influx from sarcoplasmic reticulum (SR) ⇨ ***Contraction***. ***Example*** ⇨ β_1 and β_2 adrenoceptors.

☞ **G_i (Inhibitory)** ⇨ ***Inhibits*** adenylate cyclase ⇨ ***Decrease*** cAMP ⇨ ***Decrease*** Ca^{2+} ⇨ Inhibition. ***Example*** ⇨ α_2 adrenoceptors.

☞ **G_q (Stimulatory)** ⇨ ***Activate*** phospholipase-C (PLC) ⇨ PLC break phosphatidylinositol bisphosphate (PIP_2) into Inositol triphosphate (IP_3) and Diacylglycerol (DAG) ⇨ IP_3 ***increase*** Ca^{2+} influx from sarcoplasmic reticulum (SR) ⇨ ***Contraction***. ***Example*** ⇨ α_1 adrenoceptors.


GPCR
PLCγ1
(+)
PIP₂
DAG
Na⁺
Ca²⁺
Na⁺
(+)
ΔV_M
Ca²⁺
IP₃
Ca²⁺
(+)
IP₃R
SR
Ca²⁺
Contraction

G_q


1. Norepinephrine binds to its receptor
Norepinephrine
Receptor
Adenylate cyclase
Ion channel
Plasma membrane
α
β
γ
α
α
G-proteins
2. G-protein subunits dissociate
3. Adenylate cyclase activated
ATP
cyclic AMP
Protein kinase (inactive)
Protein kinase (active)
Opens ion channels
4. cAMP activates protein kinase, which opens ion channels
Phosphorylates proteins
Postsynaptic cell

G_s or **G_i**

Autonomic Receptors

Parasympathetic (Cholinergic Receptors)

Sympathetic (Adrenergic Receptors)

Next page

Peripheral Cholinergic
Muscarinic Acetylcholine Receptors (mAChRs)
(Muscarinic Receptors)

Stimulated by muscarine

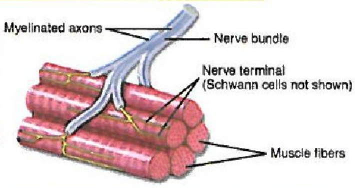
Central Cholinergic
Nicotinic Acetylcholine Receptors (nAChRs)
(Nicotinic Receptors)

Stimulated by low conc. of nicotine
Blocked by high conc. of nicotine

N_N
(Nicotinic Neural)
- Autonomic ganglia
- Adrenal medulla
- CNS

N_M
(Nicotinic Muscle)
- Neuromuscular junction (NMJ) (motor endplate) in skeletal muscle.

Opening Na^+ and K^+ channels
(Ligand-gated ion channels)



Receptor Name	Receptor Types (cellular response)	Main Locations (result of agonist binding or functional response)
M_1 (Neural)	- GPCRs (G_q) (Excitatory Effect) - Depolarization (↓ K^+)	- **CNS** (? Improve cognition and memory). - **Gastric parietal cells** in stomach (↑ acid secretion). - Ganglia (Excitatory Postsynaptic Potential; EPSP).
M_2 (Cardiac)	- GPCRs (G_i) (Inhibitory Effect) - Open K^+ channels	- **Atria of the heart** (Cardiac inhibition). - Smooth muscles. - CNS (Neural inhibition).
M_3 (Glandular / Smooth muscle)	- GPCRs (G_q) (Excitatory Effect)	- **Exocrine glands** (↑ secretions). - **Smooth muscles** (Contraction). - **Blood Vessels** (Vasodilation via NO release). - **Circular muscle** in the eye (Contraction ☞ Miosis). - **Ciliary muscle** in the eye (Contraction).
M_4 (?)	- GPCRs (G_i) (Inhibitory Effect)	- CNS (Enhancement of D_1 dopamine receptor-mediated locomotor stimulation in mice). - ? Not well known.
M_5 (?)	- GPCRs (G_q) (Excitatory Effect)	- CNS (Not known). - ? Not well known.

Sympathetic
(Adrenergic Receptors)

Alpha (α) Adrenergic Receptors

Receptor Name	Receptor Types (cellular response)	Main Locations (result of ligand binding or functional response)
α_1	GPCRs (G_q) (Excitatory Effect)	- **Vascular smooth muscle** (Vasoconstriction). - **Radial muscle** in the eye (Mydriasis). - **GIT sphincters** (Contraction). - **Pilomotor muscle** (Hair erection) - **Prostate smooth muscle** (Contraction).
α_2	GPCRs (G_i) (Inhibitory Effect)	- **Presynaptic neurons** (Inhibition neurotransmitter release from nerve ending) i.e. ***inhibit sympathetic outflow (negative feedback inhibition)***. - **Pancreas** (inhibition of insulin release).

Further subdivisions: The α_1 and α_2 receptors are further divided into α_{1A}, α_{1B}, α_{1C}, and α_{1D} and into α_{2A}, α_{2B}, and α_{2C}. This extended classification is necessary for understanding the selectivity of some drugs. For example, **Tamsulosin** is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia.

Beta (β) Adrenergic Receptors

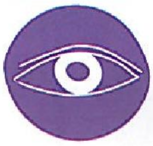
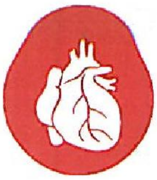
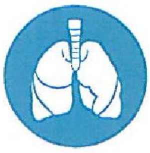
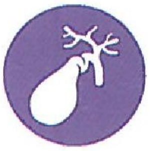
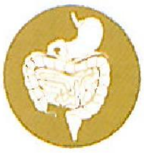
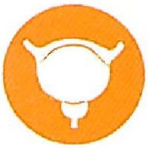
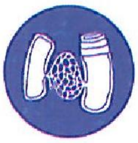
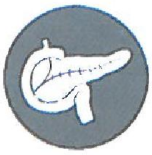
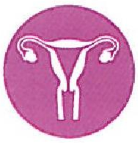
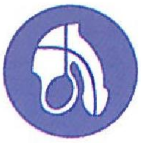
Receptor Name	Receptor Types (cellular response)	Main Locations (result of ligand binding or functional response)
β_1	GPCRs (G_s) (Excitatory Effect)	- **Heart** (↑ heart rate and force of contraction). - **Juxtaglomerular cells** in kidney (↑ Renin release).
β_2		- **Smooth muscles** e.g. bronchi, GIT, uterus & Ciliary muscle in the eye (relaxation). G_s ☞ *Inhibitory Effect!!* - **Skeletal Muscles** (? Tremors). - **Liver** (Glycogenolysis). - **Mast Cells** (Inhibition of histamine release). - Heart (↑ cardiac output, minor degree compared to β_1).
β_3		- **Fate tissues** (↑ Lipolysis and thermogenesis).

N.B: ☞ β_1 ⇨ Gs ⇨ Increase cAMP in Cardiac muscle ⇨ Contraction of muscle (Excitatory Action).
☞ β_2 ⇨ Gs ⇨ Increase cAMP in Smooth muscle ⇨ Relaxation of muscle (Inhibitory Action).

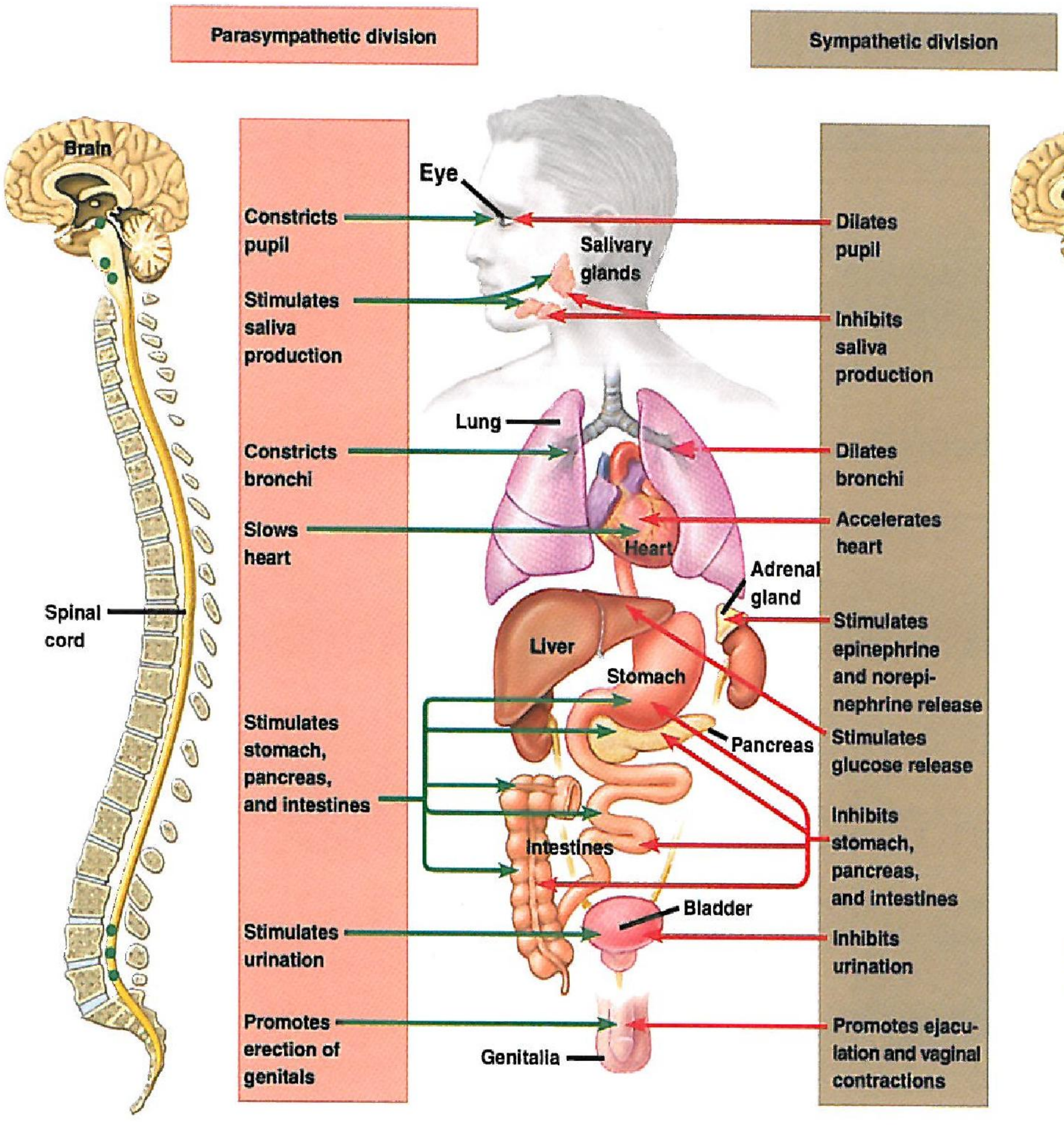
Dopamine Receptors

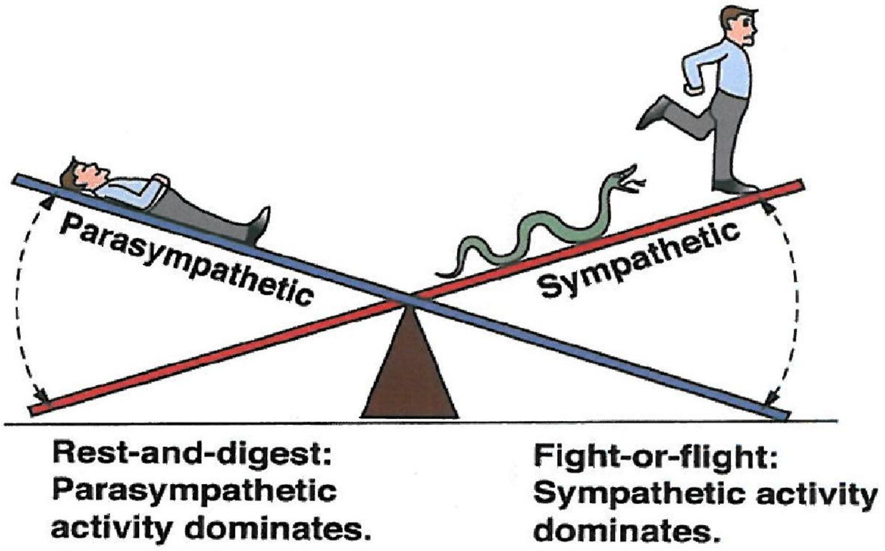
D_1 and D_5 ⇨ Brain; effector tissues, especially smooth muscle of the **renal blood vessels**.	**G_s**
D_2 ⇨ Brain; effector tissues, especially smooth muscle; **presynaptic nerve (nerve ending)**.	**G_i**
D_3 ⇨ Brain	
D_4 ⇨ Brain, Cardiovascular system	

Effect of Stimulation of Parasympathetic and Sympathetic

Organs	Parasympathetic Stimulation	Sympathetic Stimulation
	- ***Circular*** muscle contraction (M_3)⇨ ***Miosis*** - Ciliary muscle ***contraction*** (M_3)⇨ accommodation for ***near vision***	- ***Radial*** muscle contraction (α_1)⇨ ***Mydriasis*** - Ciliary muscle ***relaxation*** (β_2)⇨ accommodation for ***far vision***
	***Decrease*** *cardiac properties* (M_2): - (-ve) Inotropic (Force of contraction) - (-ve) Chronotropic (Heart rate) - (-ve) Dromotropic (Conduction in the heart)	***Increase*** *cardiac properties* (β_1): - (+ve) Inotropic (Force of contraction) - (+ve) Chronotropic (Heart rate) - (+ve) Dromotropic (Conduction in the heart)
	- Bronchoconstriction (M_3) - Stimulate bronchial secretion (M_3)	- Bronchodilatation (β_2)
	- Watery salivary secretion (M_3)	- Viscous salivary secretion (α_1)
	- Contraction of GIT wall and ↑ Motility (M_3) - Relaxation of GIT sphincters	- Relaxation of GIT wall and ↓ Motility (β_2) - Contraction of GIT sphincters (α_1)
	- Contraction of urinary bladder wall (M_3) - Relaxation of urinary bladder sphincter	- Relaxation of urinary bladder wall (β_2) - Contraction of urinary bladder sphincter (α_1)
	- Vasodilatation via release of NO (M_3)	- Vasoconstriction (α_1) (+++) - Vasodilatation on skeletal muscle (β_2) (++)
	----	- ↓ insulin release (α_2) main effect (+++) - ↑ insulin release (β_2) small effect (+)
	- Contraction (**?**)	- Relaxation (β_2) - Contraction (α_1)
	- Erection (Vasodilatation via ↑ NO) (M_3)	- Ejaculation (α_1)

- Increase lipolysis ⇨ (β_3)
- Glycogenolysis (breakdown of glycogen to glucose) ⇨ (β_2)
- Increase renin release ⇨ (β_1)

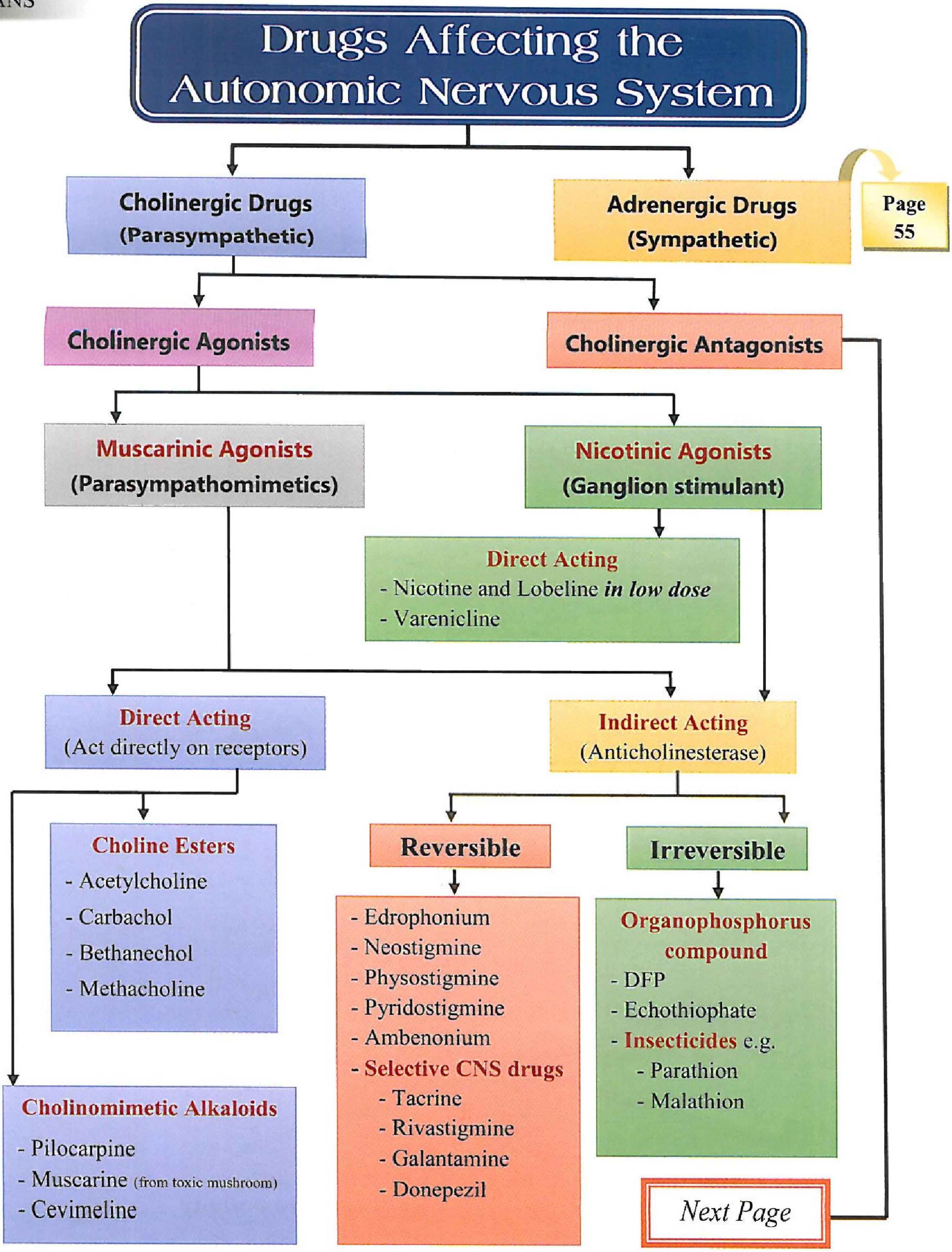

Parasympathetic division
Sympathetic division
Brain
Spinal cord
Eye
Constricts pupil
Dilates pupil
Salivary glands
Stimulates saliva production
Inhibits saliva production
Lung
Constricts bronchi
Dilates bronchi
Slows heart
Accelerates heart
Heart
Adrenal gland
Stimulates epinephrine and norepinephrine release
Liver
Stomach
Pancreas
Stimulates glucose release
Stimulates stomach, pancreas, and intestines
Inhibits stomach, pancreas, and intestines
Intestines
Bladder
Stimulates urination
Inhibits urination
Promotes erection of genitals
Promotes ejaculation and vaginal contractions
Genitalia


Parasympathetic
Sympathetic
Rest-and-digest: Parasympathetic activity dominates.
Fight-or-flight: Sympathetic activity dominates.

Q: Vascular smooth muscles non-innervated by muscarinic receptor, Explain why vasodilatation effect occurs?

A: Vasodilatation occurs when endothelium derived relaxing factor (EDRF) which is nitric oxide (NO) is released ⇨ activate Guanylate-Cyclase (GC) ⇨ increase release of cyclic guanosine monophosphate (cGMP) ⇨ Decrease Ca^{2+} ⇨ Vasodilatation (VD).

Drugs Affecting the Autonomic Nervous System



Cholinergic Drugs
(Parasympathetic)

Adrenergic Drugs
(Sympathetic)

Page 55

Cholinergic Agonists

Cholinergic Antagonists

Muscarinic Agonists
(Parasympathomimetics)

Nicotinic Agonists
(Ganglion stimulant)

Direct Acting
- Nicotine and Lobeline ***in low dose***
- Varenicline

Direct Acting
(Act directly on receptors)

Indirect Acting
(Anticholinesterase)

Choline Esters
- Acetylcholine
- Carbachol
- Bethanechol
- Methacholine

Cholinomimetic Alkaloids
- Pilocarpine
- Muscarine (from toxic mushroom)
- Cevimeline

Reversible
- Edrophonium
- Neostigmine
- Physostigmine
- Pyridostigmine
- Ambenonium
- **Selective CNS drugs**
  - Tacrine
  - Rivastigmine
  - Galantamine
  - Donepezil

Irreversible

Organophosphorus compound
- DFP
- Echothiophate
- **Insecticides** e.g.
  - Parathion
  - Malathion

Next Page

Cholinergic Antagonists

Anti-Muscarinic Agents (Anticholinergic) (Cholinergic Blockers) (Parasympatholytics)

Natural belladonna alkaloids

- Atropine
- Hyoscine

Atropine Substitutes

Selective Action on GIT

- Methantheline
- Propantheline
- Pirenzepine
- Telenzepine
- Dicyclomine
- Glycopyrrolate

Selective Action on Eye (Mydriatic)

- Homatropine
- Cyclopentolate
- Tropicamide

Antisecretory Antispasmodic Atropine Substitutes

- Hyoscine Butyl bromide
- Oxyphenonium
- Propantheline

Selective Action on CNS to Treatment Parkinsonism

- Benztropine
- Procyclidine
- Trihexyphenidyl

Selective Action on Urinary Bladder

- Flavoxate
- Oxybutynin
- Tolterodine
- Fesoterodine
- Darifenacin
- Solifenacin

Selective Action on Respiratory to Treatment Asthma

- Ipratropium
- Tiotropium

Anti-Nicotinic

Ganglionic Blockers

Depolarizing

- Nicotine and lobeline in large dose.

Non-Depolarizing (Competitive)

- Tetraethylammonium
- Pentolinium
- Pentamethonium
- Hexamethonium
- Chlorisondamine

Neuromuscular blockers

Depolarizing

- Succinylcholine
- Decamethonium

Non-Depolarizing (Competitive)

- ***Benzylisoquinolinium compound*** ⇨ - D-Tubocurarine (Curare) - Mivacurium - Atracurium - Doxacurium - Cisatracurium - Metocurine - Alcuronium
- ***Amino steroid compound*** ⇨ - Rapacuronium (Short acting)
  - Rocuronium - Vecuronium (Intermediate acting)
  - Pancuronium - Pipecuronium (long acting)
- ***Miscellaneous compound*** ⇨ Gallamine (Flaxedil)

Cholinergic Drugs (Parasympathetic)

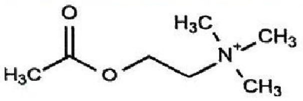
A: Cholinoceptor Agonists

1: Muscarinic Agonists (*Parasympathomimetics*)

A: Direct-Acting Muscarinic Agonists

❖ **Choline Esters :-**

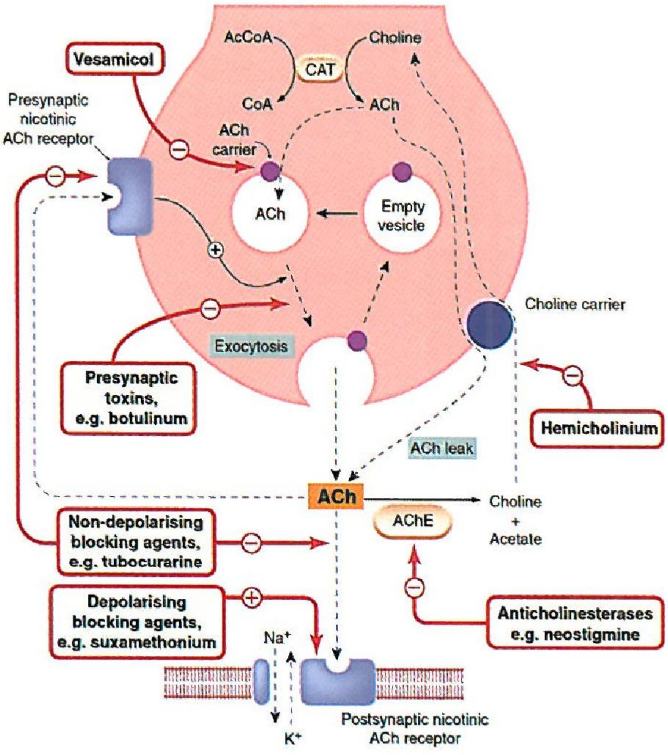
Acetylcholine (ACh)



About the Drug

- **Acetylcholine** [ah-see-teel-KOE-leen] is an *ester of* **choline** *with* **acetate**.
- **Quaternary ammonium** *compound* ⇨ *carry* (+ve) **charge** ⇨ ***polar*** ⇨ ***cannot penetrate*** **membranes** ⇨ ***not** pass* **BBB**.
- **ACh** is a **chemical transmitter**.

Synthesis, Storage and Release


AcCoA
CAT
Choline
CoA
ACh
Vesamicol
Presynaptic nicotinic ACh receptor
ACh carrier
ACh
Empty vesicle
Exocytosis
Choline carrier
Presynaptic toxins, e.g. botulinum
Hemicholinium
ACh leak
ACh
Choline + Acetate
AChE
Non-depolarising blocking agents, e.g. tubocurarine
Depolarising blocking agents, e.g. suxamethonium
Anticholinesterases e.g. neostigmine
Na⁺
K⁺
Postsynaptic nicotinic ACh receptor

Synthesis:

- **Choline** is ***transported*** *from* the **extracellular fluid** *into* the **cholinergic neuron** by **active transport** (energy-dependent carrier) **system** (**Choline** has a *quaternary* **nitrogen** and ***carries*** **+ve charge** and, ***cannot*** *diffuse* ***through*** the **membrane**).
- This ***synthesis*** can be ***inhibited by*** the **drug Hemicholinium**.
- **Choline acetyltransferase** ***enzyme*** *catalyzes* the ***synthesis*** of **Acetylcholine** ***from*** **Choline** and **Acetyl-CoA**.

Storage:

- **ACh** is ***stored*** *into* ***presynaptic*** **vesicles** to ***prevent*** **inactivation** by ***active transport***.
- The ***mature*** **vesicle** ***contains not*** *only* **ACh** *but also* **Co-transmitters**.
- *This* **Uptake** (storage) can ***inhibited by*** **Vesamicol**.

Release:

- *When* an **action potential** ***arrives*** at a **nerve** ***ending*** ⇨ ***open*** **voltage-sensitive calcium channels** on the ***presynaptic*** **membrane** ⇨ ↑ **conc.** of ***intracellular*** **Ca²⁺** ⇨ ***promote*** the **fusion** of **synaptic vesicles** *with* the **cell membrane** and the ***release*** of *their* **contents** *into* the **synaptic space** by **exocytosis**.
- This **release** can be ***blocked*** *by* **Botulinum toxin**.

Inactivation

- **Cholinesterase** **enzyme** ***breakdown*** **ACh** *into* ⇨ **Acetic acid** + **Choline**.
- **Types** of **Cholinesterase** *enzyme*:

1: ***True*** (**Acetyl**) **cholinesterase** (**AChE**) ⇨ ***found** in **all*** **ACh sites**.
2: ***Pseudo*** (**Butyryle**) **cholinesterase** (**BChE**) ⇨ ***found** in* **liver** & **plasma**.

Pharmacological Action

Heart	- (-ve) **Inotropic**, (-ve) **Chronotropic** and (-ve) **Dromotropic**.
Blood vessels	- **M_3 receptor** in ***endothelium*** are ***stimulated*** *with* **ACh** ⇨ *indirect action* via **(EDRF)** ↑ **NO** ***formation*** ⇨ **VD** ⇨ **Hypotension.**
GIT	- ***Stimulates*** **intestinal secretions** and **motility (peristalsis).** - ***Relaxation*** of **sphincters.**
Urinary bladder	- ***Contraction*** of **detrusor muscle** (wall). - ***Relaxation*** of **sphincter.**
Bronchi	- **Bronchoconstriction.** - ***Stimulates*** **bronchial secretion.**
Eye	- ***Contraction*** of **circular muscle** ⇨ **miosis.** - ***Contraction*** of **ciliary muscle** ⇨ ***accommodation*** for **near vision**
Exocrine glands	- ***Increase*** ***all*** **secretions** e.g. **lacrimation** and **salivation.**
Nicotinic Receptors	- N_N ⇨ ***Stimulate*** **ganglia** and **adrenal medulla** ⇨ ↑ ***release*** of **adrenaline** and **nor-adrenaline** ***from*** **adrenal medulla.** - N_M ⇨ ***Stimulation*** of **motor endplate (MEP)** ⇨ **muscle twitches**

Therapeutic Uses

- **Not Used Clinically** ☞ *due to:*
  - ***Multiplicity*** of **action** (***Non-selective***) act on ***all*** **ACh receptors.**
  - ***Short*** **duration** *due to* ***rapid*** **inactivation** by **cholinesterase enzyme.**
- **N.B:** ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

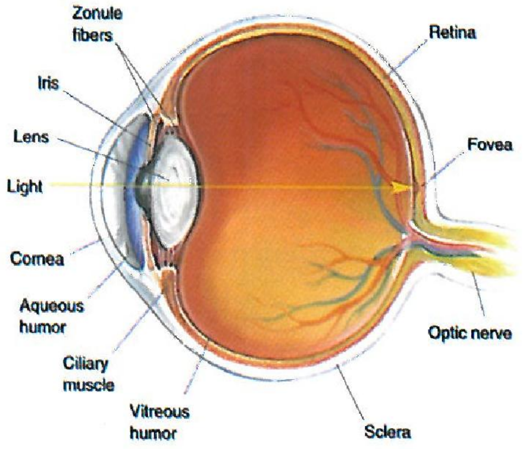
Carbachol (Isopto® Carbachol)

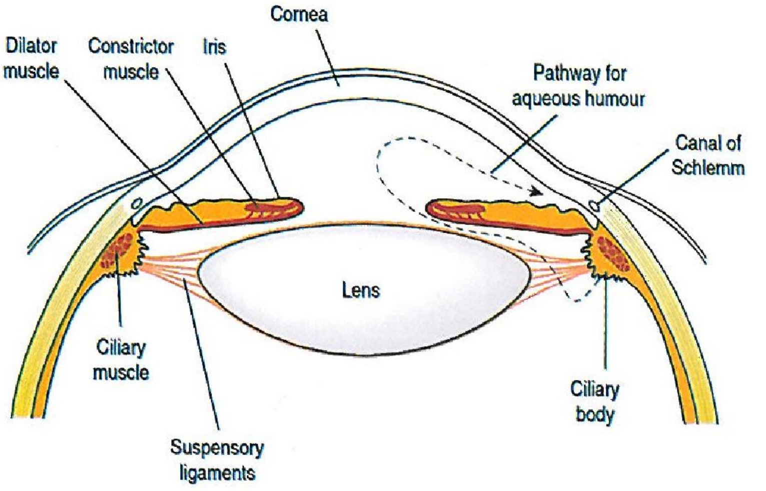
About the Drug

- **Carbachol** [KAR-ba-kole], also known as **Carbamylcholine**.
- ***Ester*** *of* **Choline** *with* **Carbamic acid**.
- **Totally** ***resistant*** to **two** ***types*** of **cholinesterase enzyme.**
- ***Rarely*** **used therapeutically** ***except*** in the **eye** as a **miotic agent** due to ☞
  - ***Longer*** **half-life.**
  - ***Non-Selective*** ⇨ act on **nicotinic** and **muscarinic** ***receptors***.

Therapeutic Uses

- ***Used*** **rarely** **except** in **eye drops** to ***treat*** **Glaucoma** ⇨ *Cause* **miosis** ⇨ ***increase*** **outflow** of **aqueous humour** *through* **canal** of **schlemm** ⇨ ***decrease*** **intraocular pressure (IOP).**


Zonule fibers
Iris
Lens
Light
Cornea
Aqueous humor
Ciliary muscle
Vitreous humor
Sclera
Optic nerve
Fovea
Retina


Cornea
Dilator muscle
Constrictor muscle
Iris
Pathway for aqueous humour
Canal of Schlemm
Lens
Ciliary muscle
Suspensory ligaments
Ciliary body

Bethanechol (Urotone®)

About the Drug

- **Bethanechol** [be-THAN-e-kole], is an *ester* of **β-methyl choline** *with* **carbamic acid**.
- ***Totally*** **resistant** to **two** *types* of **cholinesterase enzyme.**
- ***Selective to*** **muscarinic** ***receptors.***

➢ **Major Action on GIT and Urinary Bladder (UB):**

- In **GIT** ⇨ ***Increase*** **motility.**
- In **UB** ⇨ ***Contraction*** **wall** and ***relaxation*** **sphincter** ⇨ **urination.**

Therapeutic Uses

- ***Postoperative*** **non-obstructive GIT disorder** to ***prevent*** **constipation.**
- ***Postoperative*** **non-obstructive urinary tension.**
- **Gastro-paresis** (paresis of the stomach; i.e. delayed gastric emptying).
- *N.B:* It has about a **1-hour *duration*** of ***action***.

Methacholine (Provocholine®)

About the Drug

- **Methacholine** [meth-a-KOE-leen] is an *ester* of **β-methyl choline** *with* **acetic acid**.
- ***Selective to*** **muscarinic** ***receptors.***

Therapeutic Uses

- **Used** in **Bronchial Challenge Test** (or **Methacholine Challenge Test**) to ***diagnose*** **asthma** (↑ asthma when inhaled due to it act on M_3 in bronchi ⇨ cause bronchoconstriction).

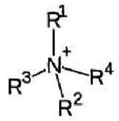
Side Effects

- **Cardiovascular effects**, *such as*:
  - **Bradycardia** and **hypotension** (**M_2**).

➢ **Properties of Choline Esters:**

Choline Esters	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine	++++	+++	+++
Carbachol	**Negligible**	++	+++
Bethanechol	**Negligible**	++	**None**
Methacholine	+	++++	**None**

- ***All*** **choline esters** are ***quaternary*** **ammonium compounds.**
  - ☞ I.e. ⇨ ***Carry*** **charge** ⇨ **Polar** ⇨ ***Don't*** **pass BBB** ⇨ ***No*** **CNS effect.**



❖ Cholinomimetic Alkaloids :-

Pilocarpine (Isopto® Carpine)

About the Drug

- **Pilocarpine** [pye-loe-KAR-peen] is an **alkaloid** of **plant origin** (***Pilocarpus leaflet***).
- ***Tertiary amine*** **alkaloid** ⇨ ***Not*** **carry charge** ⇨ ***non*-polar** ⇨ ***lipid*** **soluble** ⇨ ***pass*** **BBB** ⇨ **CNS side effect.**
- ***Stable*** to **hydrolysis** by **cholinesterase enzyme.**
- It ***shows*** **muscarinic effect *without*** having *significant* **nicotinic effect.**

Pharmacological Action

Eye (Main action)	☞ ***Penetrate*** **cornea** *because* it is **non-polar** ⇨ *produces rapid* **miosis** and ***contraction*** of the **ciliary muscle** ⇨ ***accommodation*** *for near* **vision.**
GIT	- ***Increase*** **motility.**
U.B.	- ***Increase*** **urine excretion.**
Bronchi	- **Bronchoconstriction.**
Ex. gland	- ***Potent*** **stimulators** of **secretions**; such as sweat, tears & saliva.

Therapeutic Uses

- *Treatment of* **Glaucoma** (*drug of choice* for **emergency** *lowering* of **IOP**).

☞ It *cause* **miosis** and *contracts* to **ciliary muscle**, it *opens* the **trabecular meshwork pores** and *facilitate* **out flow** of **aqueous humour** *into* the **canal** *of* **schlemm** ⇨ ↓ **IOP** (Intraocular pressure).

Side Effects

- **CNS** *side effect* ⇨ **CNS** *disturbance*.
- **Sweating** and **salivation**.

Notes

- The **miotic** *action* of **Pilocarpine** is also *useful* in *reversing* **mydriasis** *due to* **Atropine**.
- *Topical* **carbonic anhydrase inhibitors**, *such as* **Dorzolamide** and **β-adrenergic blockers** *such as* **Timolol**, are *effective* in *treating* **Glaucoma** ***but*** are ***not*** **used** for **emergency** *lowering* of **intraocular pressure**.

Q: Pilocarpine drug of choice for emergency lowering of IOP of glaucoma?

Cevimeline (Evoxac®)

Therapeutic Uses

- **Cevimeline** [se-VI-me-leen] is an **oral drug** ***used*** in **dry eye** and **dry mouth** (**xerostomia**) *associated with Sjögren's syndrome*.
- *N.B*: **Sjögren's** [SHOH-grinz] **syndrome** is an **autoimmune disease** in which **immune cells** *attack* and *destroy* the **exocrine glands** *that produce* **tears** and **saliva**.

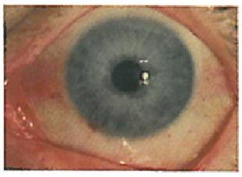
Dry mouth

Side Effects

- **Nausea, vomiting, diarrhea,** *excessive* **sweating, rash** *runny* **nose,** *blurred* **vision,** *difficulty* **breathing** and **headache**.

Contra indication

- **Patients** with *history* of **heart disease, asthma, kidney stones** or **closed angle glaucoma**.



Dry eye

B: Indirect-Acting (Anticholinesterase)

- *Not* **act** *on* **receptors** *but* **act** *on* **cholinesterase enzyme** ⇨ *inhibit* **AChE** ⇨ ↑ **ACh.**

Reversible Anticholinesterase (AChE inhibitors)

- **Binds** *reversibly* to the **active center** of **acetyl cholinesterase** (**AChE**) **enzyme** by **hydrogen** *bond* (short acting) and *weak* **covalent** *bond* (medium acting) ⇨ *inactivate* **cholinesterase enzyme** *due to* **conformational** *change*.
- It *indirectly* **stimulates** *both* **nicotinic** and **muscarinic acetylcholine** *receptors*.

Short-Acting AChE inhibitors

Edrophonium (Enlon®)

Pharmaco Kinetics

- **Edrophonium** [ed-row-FOE-nee-um] is a *quaternary* **amine** ☞ **actions** are *limited* to the **periphery** (*not pass* **BBB**).
- It is *rapidly* **absorbed** and has a *short* **duration** of **action** *due to* ***rapid*** **renal elimination**.
- *Onset of action* ☞ **IV** (30 *to* 60 seconds), **IM** (2 *to* 10 minutes).
- *Duration of action* ☞ **IV** (5 *to* 10 minutes), **IM** (5 *to* 30 minutes).
- *Half-life* ☞ 7 *to* 12 minutes.
- *Elimination time* ☞ 33 *to* 110 minutes.

Therapeutic Uses

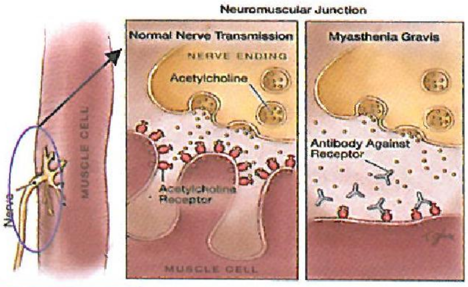
1: ***Diagnosis of*** **myasthenia gravis** ☞ **IV *injection*** of **Edrophonium** ⇨ ***rapid*** **increase** in **muscle *strength***.

- **N.B:**
  - ***Excess*** of **drug** may *provoke* a **cholinergic crisis** (is an over-stimulation at a neuromuscular junction due to an excess of ACh) ☞ **Atropine** is the ***antidote***.
  - **Enlon-Plus®** ☞ **Edrophonium** + **Atropine**.
  - ***Because*** of its ***short duration*** of **action**, it is ***not recommended*** *for* ***maintenance*** **therapy** in **myasthenia gravis**.

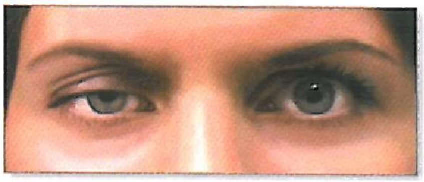
2: **Antidote *for* curare or curare like agents** (**Neuromuscular blockers**) ☞ to ***reverse*** the **effects** of ***certain*** **medications** *used to* ***prevent*** **muscle contractions** *during* **surgical procedures** e.g. **Gallamine** & **Tubocurarine**

3: **Unaccepted uses**: ***used*** to ***terminate*** **supraventricular tachycardia** *but* has ***generally*** been ***replaced*** by other **antiarrhythmic agents**.

Myasthenia Gravis (MG): Is an ***autoimmune*** **disease** in which **antibodies *break*** **nicotinic receptor** at **MEP** so ***fewer*** **receptor** are ***available*** for ***interaction*** *with* **ACh** ⇨ *causing* **muscle weakness** and ***relapse*** of **eyelid**.



Ptosis (drooping of the eyelid)



Medium-Acting AChE inhibitors

Neostigmine (Prostigmin®)	**Physostigmine** (Antilirium®)
- **Neostigmine** [nee-oh-STIG-meen] is a ***synthetic quaternary amine*** compound.	- **Physostigmine** [fi-zoe-STIG-meen] is a ***naturally tertiary amine*** alkaloid.
- ***Polar*** ⇨ ***Not*** **Lipid soluble**. - ***Not Pass*** **BBB** ⇨ ***No*** **CNS effect**. - ***Effect*** on **skeletal muscle** (+++). - ***Moderate*** **duration** of **action** (0.5 to 2 hours).	- ***Non polar*** ⇨ **Lipid soluble**. - ***Pass*** **BBB** ⇨ **CNS effects**. - ***Effect*** on **skeletal muscle** (+). - ***Moderate*** **duration** of **action** (0.5 to 2 hours).
Uses	**Uses**
- ***Manage*** **symptoms** *of* **myasthenia gravis**. - ***Stimulate the*** **bladder** *and* **GIT** in paralytic ileus and atony of urinary bladder after surgery. - **Curare poisoning** (antidote for curare or curare like agents).	- **Antidote** *for* **atropine** to reverse the central and peripheral side effect of atropine e.g. dry mouth, blurred vision, Flushing, etc. - ***Increase*** **GIT motility** and **stimulate bladder**. - Used in glaucoma and Alzheimer's Disease *but* ☞ not recommended (***Unspecific***).
Adverse Effects	**Adverse Effects**
- ***Include those of generalized*** **cholinergic *stimulation*** e.g. salivation, hypotension, nausea, flushing, abdominal pain and diarrhea. - ***Not*** **cause CNS *side effects***. - **C/I** in **intestinal** or **urinary bladder *obstruction***.	- **Convulsion** and **bradycardia**. - ***Paralysis of*** **skeletal muscle** (*rarely*) *due to* accumulation of ACh at the skeletal neuromuscular junction as a result of inhibition of cholinesterase enzyme.

Pyridostigmine (Mestinon®)

Ambenonium (Mytelase®)

- **Pyridostigmine** [peer-id-oh-STIG-meen] and **Ambenonium** [am-be-NOE-nee-um] are ***quaternary ammonium*** **compounds** ⇨ **Polar** (not cross BBB).
- ***Slightly longer*** **duration** of **action** than **Neostigmine** {**Pyridostigmine** (3 to 6 hours), **Ambenonium** (4 to 8 hours)}.
- ***Used*** in the ***chronic*** **management** of **myasthenia gravis**.
- ***Adverse effects***: *Similar to* **Neostigmine**.

Distigmine (Ubretid®)

- **Distigmine** [dee-STIG-meen] is ***similar*** to **Neostigmine** *but* has a ***longer*** **duration** of **action**.
- **Distigmine** has a ***greater*** **risk** of *causing* **cholinergic crisis** so, *rarely* **used** as a ***treatment*** for **myasthenia gravis**.
- ***Used*** in **paralytic ileus & increase atony of urinary bladder *after* surgery**.

Demecarium (Humorsol Ocumeter®)

- **Demecarium** [deh-meh-KARE-ee-um] is a drug that ***used*** **topically** in **eye drops** for ***treatment of*** **glaucoma** in ***cats***, ***dogs***, and ***other animals*** (rarely used in human due to may cause retinal detachment).

Anticholinesterase with Selective CNS Effects

Tacrine | Donepezil (Aricept®) | Rivastigmine (Exelon®) | Galantamine (Reminyl®)

- **Tacrine** [TAK-reen] was the ***first*** to *become* **available**, ***but*** it has been ***replaced*** *by others* because of its **hepatotoxicity**. **Despite** the ***ability*** of **Donepezil** [doe-NEP-e-zil], **Rivastigmine** [ri-va-STIG-meen], and **Galantamine** [ga-LAN-ta-meen].
- ***Uses***: ***Delay*** the **progression** of **Alzheimer's disease** (Deficiency of cholinergic neurons in the CNS).
- **Adverse effects**: ***GI distress*** is their primary adverse effect.

Irreversible Anticholinesterase (Organophosphate Compounds)

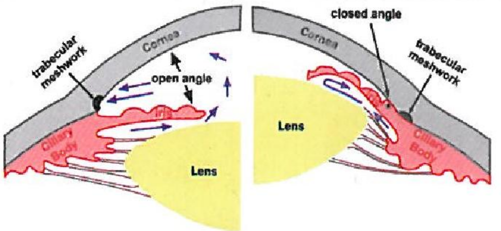
- A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released.
- Many of these drugs are extremely toxic and were developed by the military as nerve agents.

Diisopropyl fluorophosphate (DFP)

- It is ***highly*** **lipid soluble** and is well ***absorbed*** across ***all*** **membranes**.
- *May* ***used*** in ***treatment*** of **chronic open-angle glaucoma** (*rarely* used).

Echothiophate (Phospholine®)

- **Echothiophate** [ek-oe-THI-oh-fate] is an **organophosphate** that ***covalently*** **binds** via its **phosphate group** at the ***active*** **site** of **AChE** ⇨ the **enzyme** is ***permanently*** **inactivated** ⇨ ***restoration*** of **AChE activity** *requires* the ***synthesis*** of ***new*** **enzyme**.
- ***Used*** **topically** in ***treatment*** of **open-angle glaucoma**.



Insecticides (For Example)

Malathion (Ovide®) | Parathion (Folidon®)

- **Malathion** [mal-a-THYE-on] is ***less*** **toxic** than **Parathion** [par-a-THYE-on] in ***mammalian*** **species**.
- They are ***highly*** **absorbed** *via* **skin, mucous membranes** and **orally**.

War Gases (Toxic Gases)

- **Organophosphate nerve gases** *such as* **Tabun (GA)**, **Sarin (GB)** and **Soman (GD)**.
- **Nerve gases** *binds* ***covalently*** to **AChE** ⇨ the **enzyme** is ***permanently*** **inactivated** ☞ **Acetylcholine *accumulates*** ☞ **nerve impulses** ***cannot*** be **stopped**, *causing* ***prolonged*** **muscle** ***contraction*** ☞ **Paralysis** ***occurs*** and **death** may ***result*** since the **respiratory muscles** are ***affected*** (respiratory arrest)
- ***Signs*** includes (**DUMBBELSS**) ⇨ **D**iarrhea, **U**rination, **M**iosis, **B**radycardia, **B**ronchoconstriction, **E**mesis, **L**acrimation, **S**alivation and **S**weating.

➤ Treatment of Toxicity of Irreversible Anticholinesterase:-

1) **Pralidoxime** (Protopam®) ⇨ **Pralidoxime** [pral-i-DOX-eem] ***reactivates inhibited*** **AChE** by ***displaces*** the **phosphate** *group* of the **organophosphate** and ***regenerates*** the **enzyme**. It is ***unable*** to **penetrate** *into* the **CNS** (not useful in treating the CNS side effects).
   - **Pralidoxime IV dose: (25-50 mg/kg)**
     - ***Initial* dose:** 1 to 2 g as an IV infusion in 100 mL of normal saline, over 15 to 30 minutes.
     - ***Second* dose:** 1 to 2 g may be indicated after about 1 hour.
     - ***Additional* doses:** may be given every 10 to 12 hours if muscle weakness persists.
2) **Atropine** ⇨ ***blocking*** **muscarinic receptors** (Prevent peripherally and centrally muscarinic side effect due to it pass BBB) (***see next page***).

   DuoDote® ⇨ Atropine + Pralidoxime ⇨ in ***one ampoule*** for **injection**

3) **Diazepam** (Valium®) ⇨ **Anticonvulsant** (reduce the persistent convulsion) (***seen later***).
4) **Oxygen supply** ⇨ ***Artificial*** **respiration**.

2: Nicotinic Agonists (*Ganglion Stimulants*)

Nicotinic Receptors

- N_N ⇨ **Adrenal medulla, CNS** and **autonomic ganglia** (symp. and parasympathetic).
- N_M ⇨ **Neuromuscular junction** (NMJ).

Nicotine (Nicorette®)	**Lobeline**

- **Nicotine** [NIK-oh-teen] and **lobeline** [lo-BEE-leen] are ***stimulates*** **nicotinic receptors** *in small* **dose**.
- **Nicotine** ***stimulate*** **nicotinic receptors** (depending on the dose), the ***stimulatory*** **effects** are ***complex*** and ***result*** *from* ↑ ***release*** of **neurotransmitters**. (***See* CNS *chapter***).
- Nicorette® products (chewing gum, lozenges, patches, oral spray inhalator, sublingual tablets and nasal spray) ***aid in*** **smoking** ***cessation***.
- ***Stimulate*** **nicotinic receptor** on *both* **sympathetic** and **parasympathetic** ***ganglia***.
  - ☞ **Sympathetic** ***stimulation*** ⇨ ***increase*** **adrenaline** and **noradrenaline** ***release*** ⇨ ***increase*** **cardiac force** ⇨ ***increase*** **cardiac output (CO)** ⇨ **VC** ⇨ ***increase*** **blood pressure (BP)**.
  - ☞ **Parasympathetic** ***stimulation*** ⇨ ***increase*** **motility** and ***all*** **secretion**.

Varenicline (Chantix®) (Champix®)

- Chantix® in the USA and Champix® in Canada Europe and other countries.
- **Varenicline** [var-EN-ih-kleen] is an oral drug ***used to*** **quit smoking** (***treat nicotine addiction***). ***Act as*** a ***partial*** **agonist** in the **nicotinic receptors** (especially CNS receptors) ⇨ ***Stimulates*** the **receptors** *without* ***producing*** a ***full*** **effect** *like* **nicotine**.

Dose

- **Days 1** *to* **3** ⇨ **0.5 mg** orally ***once*** a day.
- **Days 4** *to* **7** ⇨ **0.5 mg** orally ***twice*** a day.
- **Days 8** *to* **end** of **treatment** ⇨ **1 mg** orally ***twice*** a day.

☞ Patients ***should be*** **treated** with Varenicline for **12 weeks**.

- ***Most common adverse effects*** ☞ **Nausea, vomiting, headache, constipation, sleep disturbance** and **unusual dreams**. **Varenicline** are **category C *in pregnancy***.
- In 2007, the FDA received post-marketing reports of thoughts of suicide in people using **Varenicline**.
- In 2009, the FDA requires **Varenicline** to carry a **black box warning** that the drug should be stopped if suicidal behaviour are developed.

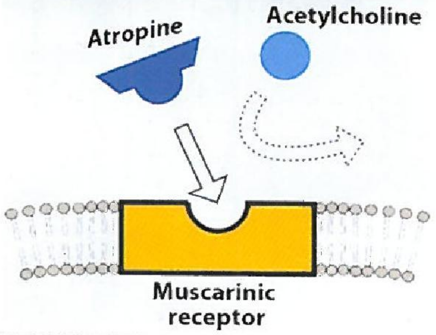
B: Cholinoceptor Antagonists (Parasympatholytics)

1: Antimuscarinic Agents - Anticholinergic - Cholinergic Blockers

A: Natural Belladonna Alkaloids

Atropine (dl-Hyoscyamine) (Isopto® Atropine) (AtroPen®)

About the Drug



- **Atropine** [A-troe-peen] is a ***tertiary amine*** **belladonna alkaloid.**
- Has ***high*** **affinity** to **muscarinic** ***receptor***
- It's ***competitive*** **antagonist** ⇨ ***prevent*** **ACh** *from* ***binding*** to those **sites.**
- It's ***pass*** **BBB** ⇨ **CNS effects.**
- It *has* **peripheral** and **central** *effect.*
- **Antidote** *for* **cholinergic** ***agonists.***

Pharmaco Kinetics

- ***A*bsorbed** *from* ***all*** **sites.**
- ***D*istributed** ***all over*** the **body.**
- ***M*etabolized** ***mainly*** in **liver.**
- ***E*limination** in **urine.**

Pharmacological Action

- ***Passive*** **Mydriasis** ⇨ *due to* ***weakening*** of constrictor (circular) pupil muscle (allow radial muscle to contract).
- **Cycloplegia** ⇨ paralysis of the ciliary muscle ⇨ ***loss*** of the ***ability*** to **accommodate.**
- ***Increase*** **IOP** in **patient** *with* **closed angle glaucoma** ⇨ *due to* ***narrowing*** of **anterior chamber angle.**
- ***Decrease*** **lacrimation** ⇨ **Dry** or **sandy eye.**

In small dose	In high dose
A) Bradycardia: (initial ↓ heart rate) ⇨ due to: **1:** ***Central*** **activation** of **vagal afferent** ***outflow.*** **2:** ***Blocking*** of M_1 **receptor** on the ***inhibitory*** **presynaptic neuron** ⇨ ↑ **ACh** ⇨ M_2. **B)** ***Minimal effect*** **on blood vessels.**	**A) Tachycardia:** (moderate ↑ heart rate) ⇨ due to ***blocking*** the **muscarinic receptors** (M_2) *on* **sinoatrial (SA) node.** **B) Vasodilatation** ***effect:*** especially in facial area ⇨ Atropine flush.

{Antispasmodic Effect}

- ***Inhibit*** **GIT** ***motility*** ⇨ ***decrease*** **tone** ⇨ ***relaxation*** of **wall.**
- ***Not*** **significance** ***effect on gastric*** **HCl** ***production:***
  - ☞ It's ***not*** **effective** in **peptic ulcer** **but** *some* **derivatives** (**Atropine substitutes**) are **used** *for* in **peptic ulcer** e.g. **Pirenzepine** and **Telenzepine** ⇨ Which are ***selective*** M_1 **antagonist** ⇨ ***decrease*** **acid** ***secretion*** with ***less*** **side effect** *than* **Atropine.**

Pharmacological **Action**

- ***Urine* retention** ⇨ *Cause* ***relaxation*** to **urinary bladder wall** and ***contraction*** to **sphincter** ⇨ **(Difficult micturition).**
- **N.B**: So it's ***contraindicated*** in **urinary tension** *especially* **urinary tension** *associated with* **prostatic hyperplasia.**

- ***Slight* bronchodilator** and ***decrease* bronchial secretion.**
- **N.B**: So it's **used** *before* **administration** of **inhalant anaesthetics** e.g. **Halothane** to ***reduce*** **secretion** in the **trachea** and the ***possibility*** of **laryngospasm.**
- **Atropine substitutes** e.g. **Ipratropium** and **Tiotropium** ⇨ ***more* effective** and ***less* side effects** (selectivity), so ⇨ **used** in **bronchial asthma.**

- ***Decrease all* secretions:**
  - ↓ **Salivation** (Xerostomia; dry mouth).
  - ↓ **Lacrimation** (Dry or sandy eye).
  - ↓ **Sweating** (↑ body temperature).
    - Cause **atropine *fever*** in **children.**

- *In **normal*** **dose** ⇨ ***little* CNS effects.**
- *In **toxic*** **dose** ⇨ **CNS excitation** (restlessness, hallucinations and disorientation).
- Has **anti-tremors effect** in **Parkinson's disease** ⇨ due to ***blocking*** **muscarinic receptors** in **brain** ⇨ ↓ ACh activity.

Therapeutic **Uses**

A) Ophthalmologic Disorders:-

1) Used *before* Eye Examination:

- **Measurement of refractive errors** (Myopia or Hyperopia).
- **Examination of retina** by *inducing* **mydriasis.**

☞ **Atropine substitute** (short-acting) e.g. **Cyclopentolate** and **Tropicamide** ***more*** **preferred** ***than*** **Atropine** in **eye *examination*** *due to **short*** **duration** of ***action***.

2) Uveitis and iritis treatment (inflammation of the uvea/iris):

- **Mydriasis** and **ciliary muscle** ***relaxation*** *desirable* in **acute inflammatory conditions** of the **iris** and **uveal *tract*.**

☞ **Atropine substitute** (long-acting) e.g. **Homatropine** ***more*** **preferred** *than* **Atropine** in ***uveitis*** and ***iritis***.

Drug	Duration of effect (days)	Usual concentration (%)
Atropine	7-10	0.5-1
Homatropine	1-3	2-5
Cyclopentolate	1	0.5-2
Tropicamide	0.25	0.5-1

Therapeutic Uses

B) Gastrointestinal Disorders:-

1) **Antispasmodic** ⇨ ***Relax*** the **GI tract.**

☞ **Atropine substitute** e.g. **Hyoscine N-Butylbromide** ***more* preferred *than* Atropine** as **antispasmodic agent.**

2) **Antidiarrheal** ⇨ *often **combined** with* **opioid antidiarrheal drug** e.g. **Diphenoxylate** (lomotil®) ⇨ **Diphenoxylate + Atropine** (the exact role of atropine is discourage abuse of diphenoxylate; atropinism).

C) Urinary Disorders:-

1) **Urinary incontinence** ⇨ ***Contraction*** **to bladder *sphincter*.**

2) **Bladder spasm after urologic surgery** ⇨ ***Relax*** **bladder *wall*.**

3) **Overactive bladder syndrome (OAB).**

☞ **Atropine substitute** e.g. **Oxybutynin** and **Solifenacin *more* selective *than* Atropine** in **urinary disorders.**

D) Cardiovascular Disorders:-

1) **Treat bradycardia** (**Atropine** cause *temporarily* ***increase*** **heart rate**)

2) **Reduce AV heart block** (*associated with* **Digitalis toxicity** or **myocardial infarction**).

Usual adult dose: 0.4 to 1 mg IV one time (repeated every 1 to 2 hours as needed to achieve an adequate heart rate or promote normal AV node conduction or within 5 to 10 minutes if the initial effect is inadequate).

Usual pediatric dose: 0.01 to 0.03 mg/kg IV every 5 minutes for 2 to 3 doses as needed.

E) Respiratory Disorders:-

1) **Preanesthetic medication**:

- **Atropine** *become* **part** of ***routine*** **preoperative medication** when **anesthetics** *such as* **halothane** were **used *due to***:
  - **Anti-secretory agent** (block salivary secretion and decrease secretion in the trachea which can accelerate reflex bronchoconstriction)
  - **Bronchodilator agent** (prevent episodes of reflex laryngospasm).
  - **Protect heart from arrhythmia** (particularly bradycardia).

Usual adult dose: 0.4-0.6 mg 30-60 minutes Pre-operative, repeat every 4-6 hours as needed.

Usual pediatric dose: 0.01 mg/kg/dose 30-60 minutes Pre-operative, repeat every 4-6 hours as needed.

F) Cholinergic Poisoning (Antidote for Cholinergic Agonists):

- **Atropine** is **used** *for* the **treatment** of **organophosphate** (insecticides and nerve gases) **poisoning, overdose** of *clinically* **used anticholinesterases** *such as* **Physostigmine** and in ***some*** *types* of **mushroom poisoning.**

Usual dose: 0.05 mg/kg/dose IV repeated every 3-5 min. as needed, doubling the dose if previous dose not treat signs of parasympathomimetic activity.

Therapeutic Uses

G) Central Nervous System Disorders:-

1) Parkinson's disease (Adjuvant therapy):

☞ **Atropine substitute** e.g. **Benztropine used** *with* **L-dopa** in *management* **Parkinson's** ***symptoms*** (*see* **CNS** ***chapter***).

2) Motion sickness:

- *Certain* **vestibular disorders** *respond to* **antimuscarinic drugs.**
- **Scopolamine** is **one** of the ***oldest*** **remedies** for **seasickness.**

Dose-Dependent Effects

0.5 mg	1mg	2mg	5mg	10mg
Slight dry mouth and slight bradycardia	Great dry mouth, slight tachycardia and slight mydriasis	Very dry mouth, tachycardia with palpitation, mydriasis, slight blurring near vision and dry skin.	Increase in previous symptoms plus disturbance of speech, difficulty in swallowing, headache and hot dry skin.	Previous symptoms to extreme degree, plus ataxia, hallucination, delirium and coma.

Side Effects

{Depending on The Dose}

- ***Most common*** **side effects** *include* dry mouth, blurred vision, "sandy eyes" tachycardia, urinary retention and constipation.
- ***Effects on the*** **CNS** *include* restlessness, confusion, hallucinations, and delirium which may progress to depression, collapse of the circulatory and respiratory systems and death.
- **Atropine** ***toxicity*** can ***overcome*** by *administration* of **Physostigmine** ⇨ ***prevent*** **peripheral** and **central Atropine** ***side effects***.

Contra indication

- **Glaucoma** *especially* closed-angle glaucoma.
- **Tachycardia.**
- **Atropine** is ***only*** **recommended** for use *during* **pregnancy** when **benefit** ***outweighs*** **risk** (**Category C**).

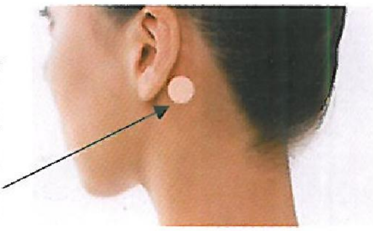
Scopolamine or Hyoscine (Transderm Scop®)

About the Drug

- **Scopolamine** [skoe-POL-a-meen], another ***tertiary amine*** **plant alkaloid**, *produces* **peripheral effects** ***similar to*** those of **Atropine.**
- ***It differs from atropine in the following***
  - It is ***more*** **potent** in **mydriasis, cycloplegia** and ***decrease*** **secretion.**
  - It is ***less*** **potent** in **heart** and **bronchial muscle.**
  - It is ***greater*** **action** on the **CNS** (produces amnesia and drowsiness).
  - It is ***longer*** **duration** of **action.**

Therapeutic Uses

- **Scopolamine** is **one** of the ***most*** **effective anti–motion sickness drugs.**
- ***The therapeutic*** **use** of **scopolamine** is *limited to* **prevention** ***of*** **motion sickness** and **postoperative nausea and vomiting.** It is available as a topical patch (Transderm Scop®) that provides effects for up to 3 days.



B: Synthetic and Semi-synthetic Atropine Substitutes

Homatropine (Isopto® Homatropine) | Cyclopentolate (Cicloplejico®) | Tropicamide (Mydriacyl®)

- **Cyclopentolate** [SIGH-kloe-PEN-toe-late] and **Tropicamide** [TROP-ik-ah-mide] ***used*** for **mydriasis** and **cycloplegia** (***before* eye examinations**).
- **Phenylephrine** (or *similar* **α-adrenergic drugs**) are ***preferred** for* **mydriasis** *if* **cycloplegia** is *not* **required**.
  - **Cyclopentolate** + **Phenylephrine** (Cyclophrine®)
  - ☞ More preferred for mydriasis with less cycloplegia effect.
- **Homatropine** [hoe-MAT-roe-peen] ***more* preferred** in **uveitis** and **iritis**.
- **Tropicamide** is *currently* **abused** (injected IV) as an *inexpensive* **euphoric deliriant drug**. It is usually ***mixed*** with **Heroin**, **Methadone** & other opioid drugs to **increase the efficacy** of heroin ***while*** **decreasing and delaying the withdrawal symptoms**.

Hyoscine (or Scopolamine) N-Butylbromide (Buscopan®)

- **Hyoscine butylbromide** [HI-oh-seen BYOU-tull-BROH-mide], ***most popular antispasmodic drug***, **relief spasms** in the **gastro-intestinal (GI)** *or* **genito-urinary (GU) tract**.

Tiemonium (Viscéralgine®)

Tiemonium [ti-moh-nee-uh m], ***antispasmodic drug*** **relief GI/GU tract spasms**.

Dicyclomine or Dicycloverine (Bentyl®)

Dicyclomine [dye-SYE-kloe-meen] or **Dicycloverine** [dye-SYE-kloe-ver-ine], ***used*** to **reduce GI cramping** *especially* **colon spasm** {**irritable bowel syndrome (IBS)**}.

Oxyphenonium (Anil®) | Propantheline (Pro-Banthine®)

- **Oxyphenonium** [OX-ee-fe-NOE-nee-um] and **Propantheline** [proe-PAN-the-leen] are ***antispasmodic drugs***.
- Also ***used*** in **stomach ulcers** in ***combination** with other* **drugs**.

Glycopyrrolate or Glycopyrronium (Robinul®)

- **Glycopyrrolate** [glye-koe-PIE-roe-late], **Anti-secretory *drug***.
- ***used*** in **anesthesia**, as a ***preoperative medication*** (reduce salivary, trachea, and pharyngeal secretions, as well as decreasing the acidity of gastric secretion).

Clidinium (Librax®)

- **Clidinium** [cli-DIN-ee-um], ***used*** for **reduce cramping** and **gastric acidity**.
- It is *commonly* ***prescribed*** in *combination with* **Chlordiazepoxide** (**benzodiazepine derivative**) for **treatment IBS**. (Librax®).

Pirenzepine (Gastrozepin®) | Telenzepine

- ***Used*** (*rarely*) in **peptic ulcer** with other drugs ⇨ ***reduces* gastric acid *secretion*** (selective M_1 receptor) (***see* GIT *chapter***).

Ipratropium (Atrovent®) | Tiotropium (Spiriva®)

- **Ipratropium** [i-pra-TROE-pee-um] and **Tiotropium** [ty-oh-TROPE-eeum] are *approved* as **bronchodilators** for *maintenance* **treatment** of **bronchospasm** *associated with* **Chronic Obstructive Pulmonary Disease (COPD)**.
- **Ipratropium** is also **used** in the ***acute* management** of **bronchospasm** in **asthma**.
- *Both* **agents** are ***delivered** via* ***inhalation*** ⇨ Because of their ***+ve charges*** (quaternary ammonium), these drugs do ***not enter*** the **systemic circulation** or the *CNS*.
- ***Duration of action***; **Tiotropium** (24 hours; once daily) ***longer*** in **duration** ***than*** **Ipratropium** (4 hours; up to four times daily).

Oxybutynin (Ditropan®)	**Tolterodine** (Detrusitol®)
Darifenacin (Enablex®)	**Fesoterodine** (Toviaz®)
Solifenacin (Vesicare®)	**Flavoxate** (Genurin S.F®)
Trospium (Spasmolyt®)	**Propiverine** (Mictonorm®)
Emepronium (Cetiprin®)	

- *All of these* **drugs** *used* to *reduces* **muscle spasms** of the **bladder & urinary tract.**
- *All of these* **drugs** *used* to *treat* **symptoms** of **overactive bladder (OAB),** such as **frequent** or **urgent urination**, **incontinence**, and **increased night-time urination.**
- *All of these* **drugs** *contraindicated* in: **urinary retention**, **gastric retention** *and* **closed-angle glaucoma.**
- **Oxybutynin** [OX-i-BUE-ti-nin] & **Tolterodine** [tol-TER-oh-deen] are ***most commonly* used.** **Oxybutynin** is *also available as* a transdermal (topical patches).
- **Darifenacin** [dar-e-FEN-a-sin] is *indicated for* the **treatment** of **OAB** *with* **symptoms** *of* **urge urinary incontinence** *in* **adults**.
- **Fesoterodine** [FES-oh-TER-oh-deen] is a **prodrug**. It is broken down into its **active metabolite**, 5-hydroxymethyl **Tolterodine**.
- **Solifenacin** [sol-ee-FEN-a-sin] is ***metabolized*** in the **liver** by the **cytochrome-P450 (CYP3A4)** ⇨ ***drug interaction***; with **LME *inhibitors***. May also ***prolong*** the **QT interval** (type of arrhythmia) ⇨ ***Contraindicated*** in patient with ***long QT interval***.
- **Flavoxate** [fla-VOX-ate] is ***indicated*** for **symptomatic** *relief* of **interstitial cystitis**, **dysuria**, **urgency**, **nocturia**, **supra-pubic pain**, **frequency** and **incontinence** as may occur in **cystitis**, **prostatitis**, **urethritis**, **urethrocystitis**/**urethrotrigonitis**.
- **Trospium** [TROSE-pee-um] should be **taken** at ***least* one hour** *before* **meals** or ***given*** *on* an **empty stomach**.
- **Emepronium** [eme-p-ROE-nee-um] may *cause* **ulceration** of **esophagus**, so it ***should be*** **taken** in **orthostatic position** with ***sufficient*** **amounts** of **liquids**.

Benztropine (Cogintol®)	**Biperiden** (Akineton®)
Trihexyphenidyl (parkinol®)	

- **Benztropine** [BENZ-troe-peen], **Biperiden** [bye-PER-i-den] and **Trihexyphenidyl** [try-hex-ee-FEN-i-dill] are used in treatment of **Parkinson's disease** in combination with other drugs. (See CNS chapter).

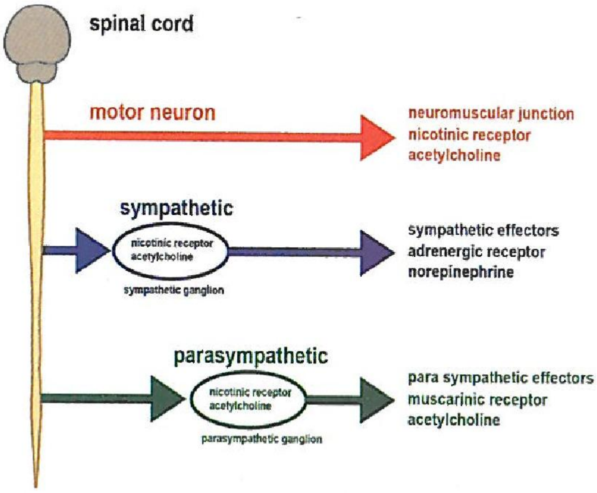
Orphenadrine (Norflex®)

- **Orphenadrine** [or-FEN-a-dreen] is a ***skeletal muscle relaxant***, relief pain due to spasm of skeletal muscle. It works by blocking nerve impulses that are sent to brain.

2: Antinicotinic Agents

A: Ganglionic Blockers (GB)

- They are **drugs** which ***block*** **nicotinic** ***receptors*** of ***both*** **sympathetic** and **parasympathetic autonomic ganglia** (***no*** **selectivity** *toward* the parasympathetic or sympathetic ganglia).
- **Ganglionic blockers** is ***rarely*** **used** ***therapeutically***, but often ***serves*** as a **tool** in ***experimental*** **pharmacology** *because* they can ***block all*** **autonomic** ***outflow***.
- ***Classification according*** *to* **mechanism** *of* **action**
  - **A) Depolarizing GB:**
    - ***First*** in **stimulation** and then in **paralysis** of ***all*** **ganglia**. I.e. **stimulation** ⇨ ***prolonged*** **stimulation** ⇨ **paralysis** of **ganglia**.
  - **B) Non-Depolarizing GB (Competitive):**
    - ***Inhibition*** of ***postganglionic*** **action** of **ACh**.


spinal cord
motor neuron
neuromuscular junction
nicotinic receptor
acetylcholine
sympathetic
nicotinic receptor
acetylcholine
sympathetic ganglion
sympathetic effectors
adrenergic receptor
norepinephrine
parasympathetic
nicotinic receptor
acetylcholine
parasympathetic ganglion
para sympathetic effectors
muscarinic receptor
acetylcholine

➢ Pharmacological Effect of Ganglion-Blocking Drugs:-

- **Sedation, tremor, choreiform movement** and **mental aberrations.**

- **Ciliary muscle** ⇨ **Primary** ***innervated*** *by* parasympathetic ⇨ ***block*** **ganglia** in **parasympathetic ciliary muscle** ***fiber*** *cause* ⇨ **Cycloplegia**.
- **Iris** ⇨ **Parasympathetic** and **sympathetic** innervation ⇨ ***parasympathetic tone usually dominates*** ⇨ ***block*** **ganglia** *cause* ⇨ **Moderate mydriasis.**

- **Arterioles** & **Veins** (**direct** ***innervated*** *by* sympathetic) ⇨ ***block*** **ganglia** *cause* ⇨ ***marked*** ↓ in **arteriolar** and **venomotor tone** ⇨ **Hypotension** (Orthostatic).
- **Heart** (**SA node** *usually* ***dominated*** *by* parasympathetic) ⇨ **Moderate tachycardia.**

- **GIT** ⇨ ***decrease*** **GI** ***secretions*** (not significant decrease in gastric acid secretion) and ***decrease*** **GI** ***motility*** ⇨ **Constipation.**

- **Urinary bladder** ⇨ ***relaxation*** of **bladder wall** and ***contraction*** of **sphincter** ⇨ **Urinary retention.**

- **Salivary gland** (Parasympathetic) ⇨ **Decrease salivation (xerostomia).**
- **Sweat gland** (Sympathetic) ⇨ **Decrease sweating.**

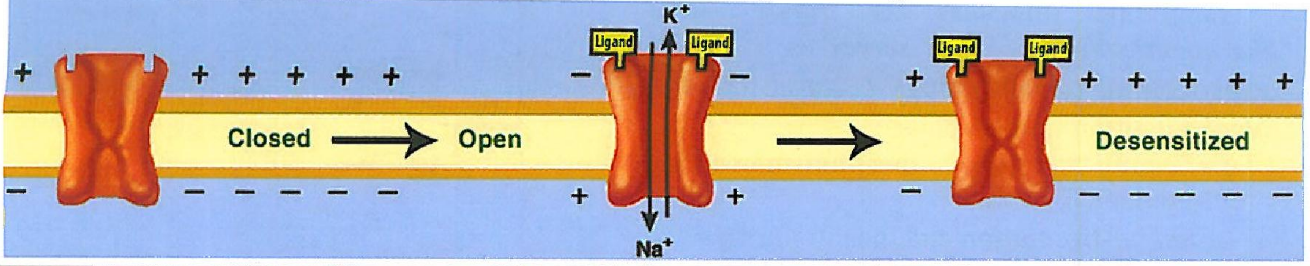
- **Erection** (Parasympathetic) ⇨ **Impotency (decrease erection).**
- **Ejaculation** (Sympathetic) ⇨ **Failure of ejaculation.**

Depolarizing Ganglionic Blockers

Nicotine

Lobeline

- **Nicotine** [NIK-oh-teen] and **lobeline** [lo-BEE-leen] are **tertiary amines** *found in* the **leaves** of **tobacco** and **lobelia** *plants*.
- They are ***stimulates*** **nicotinic receptors** in ***small*** **dose** ⇨ ***prolonged*** **stimulation** *with* **dose** ***increased*** ⇨ **paralysis** (***desensitization***) of **ganglia** (***blocker effect***).
- ***No*** **therapeutic uses**, ***except*** for **nicotine** to ***assist*** *given up* **smoking**.


K+
Ligand
Ligand
Ligand
Ligand
+ + + + + +
– –
+ + + + + + +
Closed
Open
Desensitized
– – – – – –
+ +
– – – – – –
Na+

Non-Depolarizing Ganglionic Blockers (Competitive)

Tetraethylammonium (TEA)

Hexamethonium

Pentamethonium

- **Quaternary ammonium Compounds** (**QACs**) ⇨ ***Don't*** *pass* **BBB**.
- **Used** as a **tool** in ***experimental*** **pharmacology**.

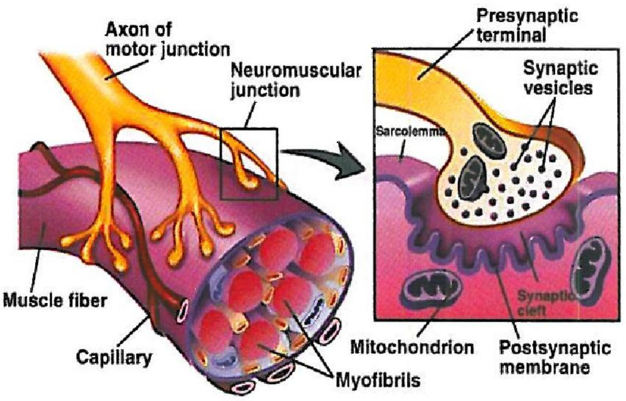
Pempidine	Tertiary amine (Non polar) ⇨ Pass BBB.

Trimethaphan (Arfonad®)	**Mecamylamine** (Inversine®)
- **Trimethaphan** [trye-METH-a-fan].	- **Mecamylamine** [meck-a-MILL-a-meen].
- ***Mono*** **sulfonium** (S^+).	- ***Secondary*** **amine**.
- ***Don't pass*** **BBB**.	- ***Pass*** **BBB**.
- ***Ultra*** **short duration** of **action** (10 to 15 min.).	- ***Longer*** **duration** of **action**.
- ***Not*** **given orally** (IV).	- **Given orally**.
- ***Treatment*** **emergency hypertension (hypertensive crisis)**.	- ***Treatment*** **hypertension**. (***moderate*** **hypertension**).
- ***Cause*** **histamine** ***release*** ⇨ **Flushing**.	- ***Not cause*** **histamine** ***release***.

B: Neuromuscular Blockers (NMB)

- These drugs ***block*** **cholinergic transmission** ***between*** **motor nerve** ***endings*** and the **nicotinic** ***receptors on the*** **skeletal muscle**.
- **NMB** are clinically ***useful during*** **surgery** to ***facilitate*** **tracheal intubation** and *provide* ***complete*** **muscle relaxation** *at* ***lower*** **anesthetic doses** (*lower anesthetic doses*; allowing for more rapid recovery and reducing postoperative respiratory depression).
- ***Classification*** **according to mechanism** ***of*** **action**;
  - A) **Depolarizing NMB**.
  - B) **Non-Depolarizing NMB** (**Competitive**).

Neuromuscular Junction


Axon of motor junction
Neuromuscular junction
Presynaptic terminal
Synaptic vesicles
Sarcolemma
Muscle fiber
Synaptic cleft
Capillary
Mitochondrion
Postsynaptic membrane
Myofibrils

Non-Depolarizing NMB (Competitive)

Benzylisoquinolinium Compounds	Amino-Steroid Compounds	Miscellaneous
Curare	**Short Acting**	**Gallamine** (Flaxedil®)
Tubocurarine (Tubarine®)	**Rapacuronium** (Raplon®)	*Add Your Updates*
Atracurium (Tracrium®)	**Intermediate Acting**	
Cisatracurium (Nimbex®)	**Rocuronium** (Esmeron®)	
Mivacurium (Mivacron®)	**Vecuronium** (Norcuron®)	
Doxacurium (Nuromax®)	**Long acting**	
Metocurine (Metubine®)	**Pancuronium** (Pavulon®)	
	Pipecuronium (Arduan®)	

- **Curare** [kyoo-RAH-ree] is the ***first*** **drug** *known to* **block** the ***skeletal*** **NMJ**, which native South American hunters of the Amazon region *used to* paralyze prey.
- **Tubocurarine** [too-boe-kyoo-AR-een] is the ***active*** **agent** of **one** of the ***forms*** of **Curare**, ***but*** it has been ***replaced*** *by* ***other*** **agents** with ***fewer*** **adverse effects**.
- **Atracurium** [a-tra-KURE-ee-um] is an intermediate-duration of action, it **cause** ***slight*** **histamine** ***release*** (**hypotension** and **bronchospasm**) and is ***metabolized*** *to* **toxic metabolite** *called* **Laudanosine** [law-DA-no-sen] ⇨ which can ***cause*** **seizures**. It has been ***replaced*** *by* its **isomer** ⇨ **Cisatracurium**.
- **Cisatracurium** [sis-AT-ra-KURE-ee-um] is ***one*** **isomers** of the **Atracurium**, *one* of the ***most commonly*** **used** ***(most popular)*** **muscle relaxant** and it have ***fewer*** **side effects** ***than*** **Atracurium** (***less*** **histamine release** and ***less*** **Laudanosine**).
- **Mivacurium** [mye-va-KURE-ee-um] is a shortest-duration of action of ***all*** **non-depolarizing NMB**, it ***cause*** **histamine release**. ***Clearance*** *by* **plasma cholinesterase enzyme** and may be ***prolonged*** in **patient** *with* **impaired renal function** (due to; decrease in cholinesterase enzyme). ***No*** **longer** ***used***.
- **Doxacurium** [doks-a-KYOO-ri-um] is **use** has ***not*** **been popular** *because* of *considerably* long duration of action, *cause* **histamine** ***release*** and ***metabolized*** *into* **Laudanosine**, ***greater*** **accumulation** in *individuals* with **renal** ***failure***.
- **Rapacuronium** [rapa- kure-OH-nee-um] is a short acting **amino-steroid compounds** and ***used*** in **short surgical operation**, ***side effects*** *include*; **hypotension**, **tachycardia** and ***fatal*** **bronchospasm**.
- **Rocuronium** [ROE- kure-OH-nee-um] and **Vecuronium** [ve-KYOO-roe-nee-um] are ***metabolized*** in the **liver** and ***clearance*** may be ***prolonged*** in **patient** *with* **hepatic** ***disease***.
- **Pancuronium** [pan-kure-OH-nee-um] is the **one** of **3 drugs** *administered* ***during*** *most* **lethal injections** in capital punishment in the United States. It is cause ***moderate*** **tachycardia** ***because***; **1)** it has moderate **parasympatholytic effect 2)** ↑ **NE** release **3)** prevent NE uptake.
  - **Lethal injection** ***components***:
    1) **Sodium Thiopental** (5 grams; 14 times the normal dose) induce unconsciousness within 10 sec. and cause respiratory depression ⇨ lead to death. (See CNS chapter)
    2) **Pancuronium Bromide** (100 milligrams) ⇨ Paralysis of respiratory muscles will lead to death.
    3) **Potassium Chloride** (100 milliequivalents) ⇨ cause rapid cardiac arrest.
- **Gallamine** [ga-L-la-mine] ***cause*** **tachycardia** and *occasionally* ↑ in **blood pressure** ***because***; **1)** it has ***strong*** **parasympatholytic effect** on the cardiac vagus nerve (Atropine like effect on the heart via block M_2 receptors). **2)** It has **sympathomimetic effect** via ↑ **norepinephrine (NE)** release (Tyramine like effect). It has ***no*** **histamine** ***release***.

- ***All*** **neuromuscular-blocking agents** are ***highly*** **polar** (not pass BBB) compounds and **inactive orally**; they **must be administered parenterally**.
- ***Pharmacokinetics properties***:

Pharmaco Kinetics

Drug	Elimination	Approximate duration of action	Approximate potency relative to Tubocurarine
Tubocurarine	Kidney (40%)	>50 min.	1
Atracurium	Spontaneous	20-35 min.	1.5
Cisatracurium	**Most Spontaneous**	25-44 min.	1.5
Mivacurium	Plasma ChE	10-20 min.	4
Rocuronium	Liver (75-90%) and kidney	20-35 min.	0.8
Vecuronium			6
Pancuronium	Kidney (80%)	>35 min.	6

* Drugs taken safely in renal and hepatic impairment are..................and.................

Mechanism OF Action

☞ **At low dose** ⇨ they *compete with* **ACh** at the **nicotinic receptors at motor end plate** *without* **stimulating** ⇨ ***inhibition*** of **muscle contraction.**

- Their **action** can be ***overcome*** can by *administration of* **cholinesterase inhibitors**, such as **Neostigmine**.

☞ **At high dose** ⇨ they ***block*** the **ion channels** of the **end plate** ⇨ ***leading to*** *further* **weakening** of **neuromuscular transmission** and ***reduce*** the **ability** of **anticholinesterase** to ***reverse*** the **action** of ***non-depolarizing*** **blockers.** *With* **complete blockade**, the ***muscle*** *does not* **respond** *to* ***direct*** **electrical stimulation.**

Pharmacological Action

Action

- *Not* **all muscles** *are* ***equally*** **sensitive** to **blockade**.
- ***Small***, ***rapidly*** **contracting muscles** of the **face** and **eye** are ***most*** **susceptible** and are ***paralyzed*** **first**, followed by the **fingers**, **limbs**, **neck**, and **trunk muscles**. *Next*, the **intercostal muscles** are affected and, lastly, the ***diaphragm***.
- The **muscles recover** in the ***reverse*** **manner**.

Drug	Effect on Ganglia	Effect on cardiac M_2 receptors	Tendency to cause histamine release
Tubocurarine	Weak block	None	Moderate
Atracurium	None	None	Slight
Cisatracurium	None	None	None
Mivacurium	None	None	Moderate
Rocuronium	None	Slight	None
Vecuronium	None	None	None
Pancuronium	None	Moderate block	None
Gallamine	None	Strong block	None

* Drugs that cause histamine release are........., ... and ....

* Drugs that cause decrease in blood pressure are ....and..........

Therapeutic Uses

- **Surgical relaxation**; As adjuvants during general anaesthesia to provide skeletal muscle relaxation.
- **Endotracheal intubation**; by relaxing pharyngeal and laryngeal muscles.
- **Electro-convulsion therapy (ECT)**; to control muscle contraction.

Side Effects

- **Tubocurarine** ⇨ **Hypotension** *due to* histamine release and ganglionic blocked.
- **Mivacurium** > **Atracurium** ⇨ **Hypotension** *due to* histamine release.
- **Gallamine** > **Pancuronium** ⇨ ***Increase* heart rate (tachycardia)**⇨*due to* vagolytic action (M_2 blocked) & ↑ NE
- **Tubocurarine**>**Mivacurium**>**Atracurium**⇨ **Bronchospasm** *due to* histamine release (C/I in asthmatic patient).

Drug Interactions

1) **Cholinesterase Inhibitors**: *such as* **Neostigmine** and **Physostigmine**.
   - Cholinesterase inhibitors can overcome the action of non-depolarizing neuromuscular blocker.
   - If the neuromuscular blocker has block the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade.
2) **Inhaled Anesthetics**: *such as* **Halothane** and **Desflurane**.
   - Inhaled anesthetics enhance non-depolarizing NMB effect by exerting a stabilizing action at the NMJ ☞ ***Additive effect***.
   - These agents sensitize the NMJ to the effects of neuromuscular blockers.
3) **Aminoglycoside Antibiotics**: *such as* **Gentamicin** and **Tobramycin**
   - Aminoglycoside antibiotics inhibits ACh release from cholinergic nerves by competing with calcium ions ☞ ***Synergistic effect***.
4) **Calcium Channel Blockers**: These agents may increase the neuromuscular blockade of competitive blockers.

- **Sugammadex** (Bridion®) is an **agent** *approved by* US FDA in December, 2015 for ***reversal*** of **neuromuscular blockade** by the agent **Rocuronium** or **Vecuronium** in **general anaesthesia**.

Depolarizing NMB (Non-Competitive)

Succinylcholine (Succinylcholine®)	**Decamethonium** (Syncurine®)

Pharmaco Kinetics

- **Succinylcholine** [SUX-i-nil-KOE-leen], also *known as* **Suxamethonium**.
- It is ***consists*** of **2 Acetylcholine *molecules*** that are ***linked* together**.
- It is ***duration*** of ***action*** is ***extremely short*** (<8 min) *due to **rapid*** **hydrolysis** by **plasma-ChE (Pseudocholinesterase)**.
- *N.B*: Genetic variants in which plasma pseudocholinesterase levels are low or absent lead to prolonged neuromuscular paralysis.

Mechanism OF Action

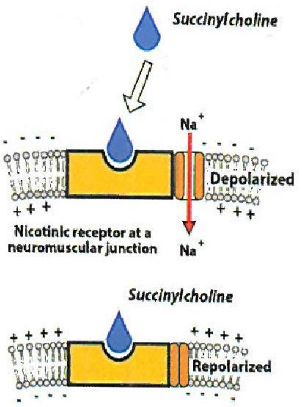
There are 2 phases to the* blocking *effect of **Succinylcholine**;

☞ **Phase I (Initial Stimulation)**

- ***Opening*** of the **Na^+ channel** *associated with* the **nicotinic receptors** ⇨ ***depolarization*** of **the receptor** ⇨ ***transient* twitching** of the **muscle** (**Fasciculations**).

☞ **Phase II (Prolonged Inhibition)**

- *During **continuous*** **depolarization**;
  - ⇨ **Receptor *desensitization***.
  - ⇨ ***Gradual* repolarization** ⇨ **Na^+ channel *blocked*** ⇨ **Paralysis** (**flaccid paralysis**)



Action	- Produce muscle ***fasciculation*** followed by ***flaccid paralysis***. - Ganglion stimulation, slight histamine release and **M_2** receptors stimulation.
Therapeutic Uses	- ***Because of its rapid onset of action used in:*** 1) **Endotracheal Intubation**. 2) **Electro-convulsion Therapy** (ECT).

Side Effects

1: Prolonged Apnea:

- **Apnea**; is a *term* for ***suspension*** of ***external*** **breathing**.
- ***Administration*** of **Succinylcholine** to a **patient** who is ***deficient in*** **plasma cholinesterase** or who has an ***atypical*** **form** *of the* **enzyme** can ***lead to prolonged*** **apnea** ⇨ ***paralysis*** of the **diaphragm**.

2: Bradycardia: (can be overcome by administration of **Atropine**);

- *Due to* **ganglionic** ***stimulation*** and **cardiac M_2 receptors** ***stimulation***.

3: Post-operative muscle pain (Myalgias): *Due to* ***initial*** **fasciculation**.

4: Increase IOP :

- *Due to* ***contraction*** of **extra-ocular muscle**; ***applying*** **pressure** to the **eye ball**

5: Hyperkalemia:

- **Patients** *with* **burns**, ***nerve*** **damage** or ***neuromuscular*** **disease**, ***closed*** **head injury** and *other* **trauma** can *respond to* **Succinylcholine** by ***releasing*** K^+ into the **blood** ⇨ may *cause* **cardiac arrest** (rare).
- ***Temporary*** **Treatments**:
  - **Regular insulin**: Which ↓ K^+ concentration in plasma (enhance entry of K^+ and prevent it is efflux from the tissues). ***Dose***: IV injection of 10-15 units of regular insulin along with 50 ml of 50% dextrose to prevent hypoglycemia.
  - **Salbutamol (β_2 agonist)**: This drug also ↓ blood levels of K^+ by promoting its movement into cells. Is administered by nebulizer (10–20 mg).

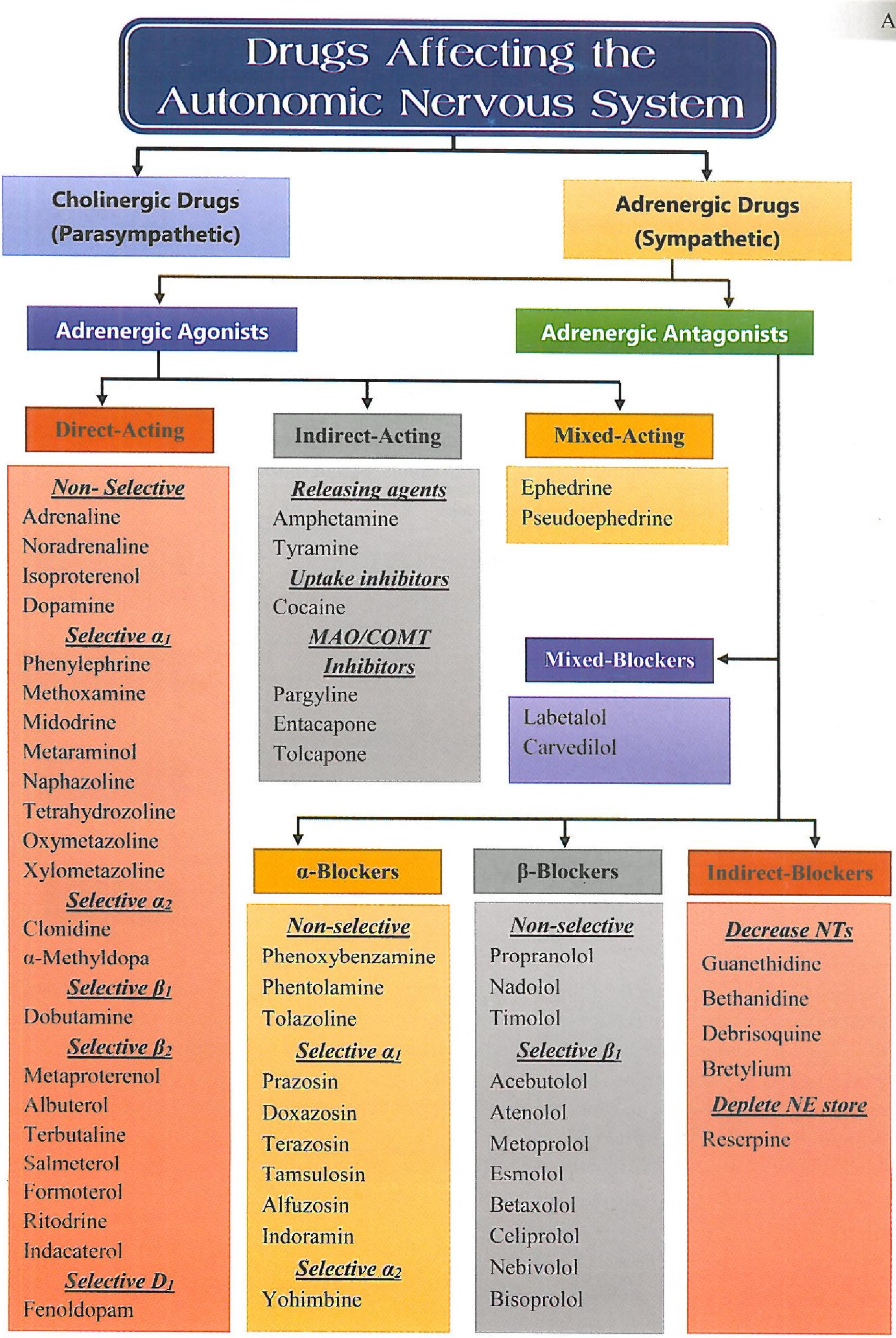
6: Malignant Hyperthermia (MH):

- Is a ***rare*** **life-threatening** *condition* that is *usually* occurs in ***susceptible*** **patients**, *exposure to* **halogenated hydrocarbon anesthetics** (e.g. **Halothane**) and **neuromuscular blocker succinylcholine**; Rabid ↑ muscle metabolism.
- **Characterized *by:***
  - ***Very*** **high temperature** and ***unexplained*** **tachycardia**.
  - **Muscle rigidity** due to ⇨ ***increase*** **muscle contraction** and ***intensive*** **pain** ⇨ due to ***abnormal increase*** of **Ca^{2+}** *from* **sarcoplasmic reticulum**.
  - **Metabolic acidosis** (the body produces excessive quantities of acid or kidneys are not removing enough acid from the body).
- **Treatments*:***
  - **Cooling patient**.
  - **Dantrolene** [DAN-tro-lean] (***Direct*** **skeletal muscle** ***relaxant***) ⇨ ***Prevent*** **release** of **Ca^{2+}** *from* **sarcoplasmic reticulum**.

- **Comparison *between* non-depolarizing muscle relaxant** and a **depolarizing muscle relaxant**:

	Rocuronium	Succinylcholine	
		Phase I	Phase II
Administration of Tubocurarine	Additive	Antagonistic	Augmented
Administration of Succinylcholine	Antagonistic	Additive	Augmented
Effect of Neostigmine	Antagonistic	Augmented	Antagonistic
Initial excitatory effect on skeletal muscle	None	Fasciculations	None
Response to tetanic stimulus	Fade	No fade	Fade
Post-tetanic facilitation	Yes	No	Yes
Rate of recovery	30-60 min	4-8 min	> 20 min

Drugs Affecting the Autonomic Nervous System



- **Cholinergic Drugs (Parasympathetic)**
- **Adrenergic Drugs (Sympathetic)**
  - **Adrenergic Agonists**
    - **Direct-Acting**
      - ***Non- Selective***
        - Adrenaline
        - Noradrenaline
        - Isoproterenol
        - Dopamine
      - ***Selective α_1***
        - Phenylephrine
        - Methoxamine
        - Midodrine
        - Metaraminol
        - Naphazoline
        - Tetrahydrozoline
        - Oxymetazoline
        - Xylometazoline
      - ***Selective α_2***
        - Clonidine
        - α-Methyldopa
      - ***Selective β_1***
        - Dobutamine
      - ***Selective β_2***
        - Metaproterenol
        - Albuterol
        - Terbutaline
        - Salmeterol
        - Formoterol
        - Ritodrine
        - Indacaterol
      - ***Selective D_1***
        - Fenoldopam
    - **Indirect-Acting**
      - ***Releasing agents***
        - Amphetamine
        - Tyramine
      - ***Uptake inhibitors***
        - Cocaine
      - ***MAO/COMT Inhibitors***
        - Pargyline
        - Entacapone
        - Tolcapone
    - **Mixed-Acting**
      - Ephedrine
      - Pseudoephedrine
  - **Adrenergic Antagonists**
    - **Mixed-Blockers**
      - Labetalol
      - Carvedilol
    - **α-Blockers**
      - ***Non-selective***
        - Phenoxybenzamine
        - Phentolamine
        - Tolazoline
      - ***Selective α_1***
        - Prazosin
        - Doxazosin
        - Terazosin
        - Tamsulosin
        - Alfuzosin
        - Indoramin
      - ***Selective α_2***
        - Yohimbine
    - **β-Blockers**
      - ***Non-selective***
        - Propranolol
        - Nadolol
        - Timolol
      - ***Selective β_1***
        - Acebutolol
        - Atenolol
        - Metoprolol
        - Esmolol
        - Betaxolol
        - Celiprolol
        - Nebivolol
        - Bisoprolol
    - **Indirect-Blockers**
      - ***Decrease NTs***
        - Guanethidine
        - Bethanidine
        - Debrisoquine
        - Bretylium
      - ***Deplete NE store***
        - Reserpine

Adrenergic Drugs (Sympathetic)

A: Adrenergic Agonists

Adrenergic Receptors
See pages 31 & 32

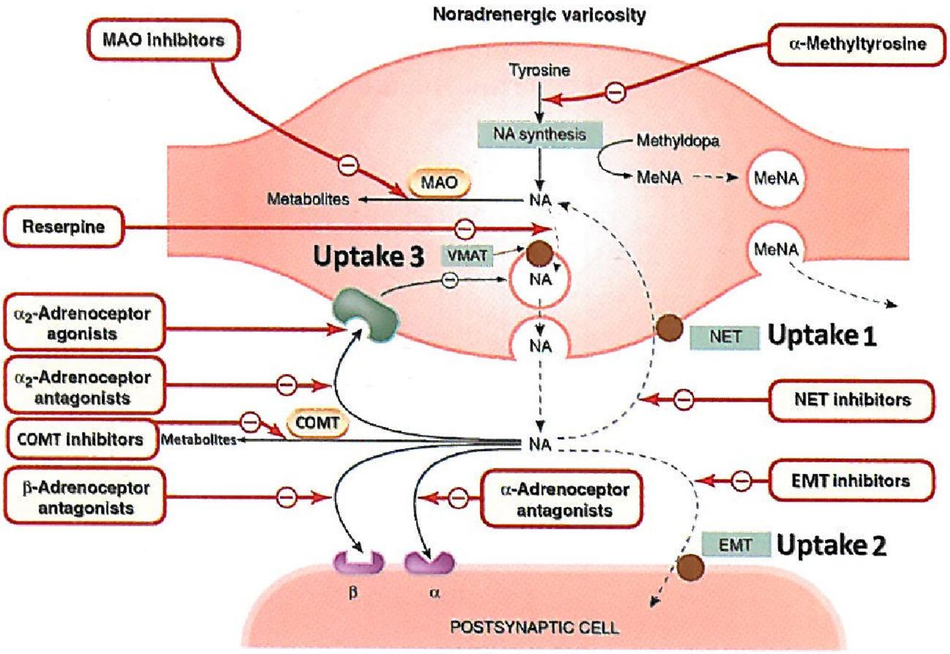
1) Direct-Acting Adrenergic Agonists

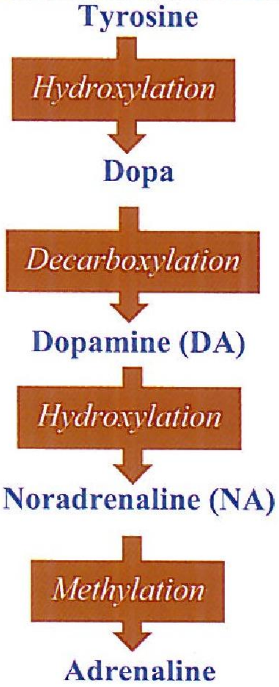
A: Non-Selective

Epinephrine or Adrenaline (EpiPen®)

About the Drug

- **Epinephrine** [ep-i-NEF-rin] is a ***natural*** **catecholamine.**
- **Norepinephrine (NE)** is ***methylated*** to *yield* **Epinephrine** in the **adrenal medulla** which is ***stored*** in **chromaffin cells.**
- ***On*** **stimulation**, the **adrenal medulla** ***releases*** *about* **80% Epinephrine** and **20% Norepinephrine** ***directly*** *into* the **circulation**.
- **L-isomer** is *about* **20 times** ***more*** **potent** ***than*** **D-isomer.**


Noradrenergic varicosity
MAO inhibitors
α-Methyltyrosine
Tyrosine
NA synthesis
Methyldopa
MeNA
MeNA
MeNA
MAO
Metabolites
NA
Reserpine
Uptake 3
VMAT
NA
NA
α₂-Adrenoceptor agonists
α₂-Adrenoceptor antagonists
NET
Uptake 1
NET inhibitors
COMT inhibitors
Metabolites
COMT
NA
EMT inhibitors
β-Adrenoceptor antagonists
α-Adrenoceptor antagonists
EMT
Uptake 2
β
α
POSTSYNAPTIC CELL


Tyrosine
Hydroxylation
Dopa
Decarboxylation
Dopamine (DA)
Hydroxylation
Noradrenaline (NA)
Methylation
Adrenaline

- **Norepinephrine Transporter (NET)** is a transporter protein integrated into the membrane of ***presynaptic*** **neurons** and it is responsible for reuptake of extracellular monoamine neurotransmitters (NTs) such as norepinephrine, dopamine and serotonin ⇨ described as "**Uptake 1**".
- **Extra-neuronal Monoamine Transporter (EMT)** is a transporter protein integrated into the membrane of ***postsynaptic*** **neurons**, it is responsible for transport monoamine NTs into postsynaptic neurons ⇨ described as "**Uptake 2**".
- **Vesicular Monoamine Transporter (VMAT)** is a transporter protein integrated into the membrane of **synaptic vesicles** of presynaptic neurons and it is responsible for transport monoamine NTs into synaptic vesicles ⇨ described as "**Uptake 3**".

Neuronal Uptake

1) **Uptake 1 (Neuronal):**
   ☞ ***Inhibited*** *by:* **Cocaine**, **Amphetamine**, **Tricyclic Antidepressants (TCAs)**
2) **Uptake 2 (Extra-Neuronal):**
   ☞ ***Inhibited*** *by:* **Cortisone.**
3) **Uptake 3 (Vesicle Uptake):**
   ☞ ***Inhibited*** *by:* **Reserpine.**

Pharmaco Kinetics

- **Epinephrine** is ***ineffective*** **orally** *due to* ***rapid*** **degradation** by **gut** and ***rapid*** **metabolism** by **liver.**
- ***Routes of administration:***
  - **SC** ⇨ **VC** ⇨ ***Slow*** **absorption** ⇨ Long duration and less toxicity.
  - **IM** ⇨ **VD** ⇨ ***Rapid*** **absorption** ⇨ Short duration and high toxicity.
  - **IV** ⇨ ***in emergency*** ⇨ rapid onset of action.
  - **Inhalation** ⇨ *in* **bronchial asthma.**
  - **Intracardiac (IC)** ⇨ *in* **resuscitation.**
  - **Eye drops** ⇨ *in* **glaucoma.**

N.B: **IV** and **IC routes** are ***very*** **dangerous** (must be diluted to 1:10,000).

- ***Duration of action:***
  - **SC** (4-6 hours) - **IM** (1-4 hours) - **Inhalation** (1-3 hours).
- ***Metabolism:***

$$\text{Epinephrine} \xrightarrow[\text{(MAO)}]{\text{Monoamine oxidase}} \text{Metabolites.}$$

$$\text{Epinephrine} \xrightarrow[\text{(COMT)}]{\text{Catechol-O-methyl transferase}} \text{Metabolites.}$$

- **Norepinephrine** and **Epinephrine metabolites** are **Metanephrine** and **Vanillylmandelic Acid** which are ***excreted*** in **urine.**
- **Vanillylmandelic Acid (VMA)** ***excreted*** in **urine** (normal adult value = 4-8mg in a day) ⇨ ***increase*** **VMA** in **urine** in **patients** *with* **pheochromocytoma** (tumour in adrenal medulla).

Pharmacological Action

Local Effects

☞ **Nose** ⇨ α_1 ⇨ **VC** ⇨ ***used*** in **epistaxis** and **congestion.**

☞ **Skin** ⇨ **used** *with* **local anaesthesia**

e.g. **Lidocaine** + **Epinephrine** ⇨ **VC** ⇨ ↓ ***absorption*** of **Lidocaine** ⇨ ***prolong*** **action** and ↓ **toxicity.**

Heart (β_1)

- (+ve) ⇨ **inotropic, chronotropic** and **dromotropic** ⇨ ↑ **cardiac output** (CO) ⇨ ↑ **systolic pressure.**

Blood Vessels (BV)

1) **Skin, mucous membranes** and **viscera (α_1): VC** ⇨ ↑ **peripheral resistance (PR)** ⇨ ↑ ***diastolic*** **pressure.**
2) **Skeletal muscles (β_2): VD** ⇨ ↓ **PR** ⇨ ↓ ***diastolic*** **pressure.**

☞ At ***low*** **doses, β_2 effects (vasodilation)** on the vascular system predominate, whereas at ***high*** **doses, α_1 effects (vasoconstriction)** are the ***strongest.***

☞ The ***cumulative*** **effect** is an ↑ in ***systolic*** **blood pressure (β_1)** and ***slight*** ↓ in **diastolic pressure (β_2).**

N.B: Epinephrine ***activates*** **β_1 receptors** on the kidney ⇨ ↑ **Renin** ***release.*** **Renin** is an ***enzyme*** *involved* in the ***production*** of **Angiotensin II** ⇨ ***Powerful*** **VC.**

- ***Powerful*** **bronchodilatation (β_2).**
- It also ***inhibits*** the ***release*** **Histamine** *from* **mast cells (β_2).**
- So it is **used** in **bronchospasm** and **anaphylactic shock.**

Pharmacological Action

- ***Relax*** **gastro-intestinal (GI)** and **genito-urinary (GU) smooth muscles.**
  - ☞ β_2 ⇨ ***Relaxation*** of **wall.**
  - ☞ α_1 ⇨ ***Contraction*** of **sphincters.**
- ***Effect*** of **Epinephrine** on **uterine smooth muscles** are *variable.*
- *Usually* it ***relaxes*** **pregnant uterus**, *especially* **during *last* month** of **pregnancy** (β_2).
- ***Selective*** β_2 **agonist** e.g. **Ritodrine** can ***used*** to **delay premature labour.**

- ***Active*** **Mydriasis ⇨ Radial muscle *contraction*** (α_1)
- *Due to **high*** **polarity** of **Epinephrine**, so ***no longer*** **used** for **glaucoma** *treatment.*

Dipivefrin (Propine®)

- **Dipivefrin** [dye-PI-ve-frin] is an **Epinephrine** ***pro-drug*** that is ***converted to*** **Epinephrine** by **esterase *enzyme*** in the **cornea.**
- **Used** to ***treat*** **open-angle glaucoma** by ↓ **intraocular pressure** (↓ aqueous humour formation and ↑ outflow).
- It is **better** ***than*** **Epinephrine** ⇨ *due to* ↑ **lipophilicity** ⇨ ***easily*** **passes** *from* **cornea** and ***penetrate*** *into* the **anterior chamber**).
- **Brimonidine** (**α_2 agonist**) also **used** in **glaucoma** (*see later*).

[Hyperglycaemic Effect]

- ↑ **glycogenolysis** in the **liver** (β_2).
- ↓ **insulin *release*** (α_2).
- ↑ **glucagon *release*** (β_2).
- **Lipolysis:**
  - ***Initiates*** **lipolysis** ⇨ by ***stimulate*** β_3 ***receptors*** in **adipose tissue** ⇨ ↑ *levels* of **cAMP** ⇨ ***stimulate*** a **hormone-*sensitive*** **lipase** ⇨ ***hydrolyzes*** **triglycerides** to ***free*** **fatty acids** and **glycerol.**

Other Actions

- **Skeletal Muscle:**
  - ***Facilitates*** **neuromuscular transmission** ⇨ by ***stimulate*** **α_1 receptors** ⇨ ↑ ***levels*** of Ca^{2+} ⇨ ***facilitate*** the ***release*** of **ACh** *from* the **motor neuron.**
  - **Muscle tremor** ⇨ **β_2 agonists** ⇨ ***stimulate*** *entry* of K^+ *into* **skeletal muscle** ⇨ ↓ ***serum*** K^+ (**hypokalemia**) ⇨ ***produce*** **muscular fluctuation (tremor)**. (The exact mechanism for tremor induction by β_2 agonists is ***still unknown***).

Therapeutic Uses

1) Bronchospasm (Acute Asthma):

- **Epinephrine** is the ***primary*** **drug *used*** *in the* **emergency** ***treatment*** of **bronchoconstriction** in **acute asthma.**
- ***Within*** a ***few*** **minutes** *after* **SC administration,** ***respiratory*** **function *greatly*** **improves.**
- ***Selective*** β_2 **agonists** are ***favored*** in the **chronic** ***treatment*** of **asthma *because*** of a ***longer*** **duration** of **action** and ***minimal*** **cardiac stimulatory effects.**

Therapeutic Uses

2) Anaphylactic Shock:

- **Epinephrine** is the ***drug of choice*** (**antidote**) for the ***treatment*** of **type-I hypersensitivity reactions** (*including* **anaphylaxis**) in *response to* **allergens** (cause excess release of chemical mediators such as histamine).
- **Epinephrine** is a ***physiological*** **antagonism** of **Histamine**:

  Histamine : **Bronchoconstriction & Vasodilatation ⇨ H_1.**
  Epinephrine: **Bronchodilatation & Vasoconstriction ⇨ β_2 & α_1.**

3) Cardiac Arrest:

- **Intracardiac *injection*** of **Epinephrine** can ***restore*** **cardiac rhythm** in **patients** *with* **cardiac arrest.**

4) Local Infiltration Anesthetics:

- **Local anesthetic** may ***combined*** *with* ***low*** **concentrations** of **Epinephrine** (for example; 1:100,000 parts) ⇨ ***local*** **infiltration anesthetics.**
- ***Benefits*** *of the* ***combination***: **greatly increases** *the* ***duration*** of **local anesthesia** by ***producing*** **VC** at the ***site*** *of* **application** and ***decrease*** **local anesthetics *toxicity*.**

5) Epistaxis (Nosebleed):

- ***Small*** **piece** of **cotton** are ***immersed*** in ***weak*** **solution** (1:10,000) of **epinephrine** and ***put*** it in **nose.**
- **Oxymetazoline** (selective α_1 agonist) is a ***drug of choice*** for **epistaxis**.

Dose

One ampoule of epinephrine (1ml) = 1:1000 (1mg in 1 ml)

- If one ampoule is diluted to 10ml (+ 9ml) = 1:10,000 (0.1 mg/1ml)

☞ **Adult dose** *for* **Cardiac Arrest:**

- **IV:** 0.5 to 1 mg (5 to 10 mL of 1:10,000) ***once***.
- May be repeated every 3 to 5 minutes as necessary.

☞ **Adult dose** *for* **Allergic Reaction:**

- **IM:** 0.1 to 0.5 mg (0.1 to 0.5 mL of 1:1000 solution).
- May be repeated every 10 to 15 minutes.

☞ **Adult dose** *for* **Acute Asthma:**

- **SC:** 0.1 to 0.5 mg (0.1 to 0.5 mL of 1:1000 solution) May be repeated every 20 minutes to once every 4 hours as needed.
- **Inhalation:** Inhalation aerosol: 160 to 220 mcg (1 inhalation) ***once***. An additional inhalation may be used after at least one min.

Side Effects

1) Cardiac Arrhythmias (Tachycardia).

2) Pulmonary Oedema.

Clarification: Tachycardia and increased systemic resistance causes excess load on left ventricle, causing pulmonary congestion. This is accompanied with mismatch in increased pulmonary artery pressure compared with pulmonary alveolar pressure, causing hydrostatic flux of fluid.

3) CNS effects: **anxiety, fear, tension, headache** and **tremor.**

4) Gangrene:

- **Gangrene** of **fingers** or **toes** *may* **occur** in **patient** *used* **local infiltration anesthetics**, *due to* **VC effects.**

Contra indication

- **Hypertension, coronary heart disease** (angina) and **arrhythmias.**
- **Hyperthyroidism** (↑ sensitivity to adrenaline) and **pulmonary oedema.**
- ***With*** **local anaesthetic** *especially* ***around*** **fingers** ⇨ *may cause* **gangrene.**

Norepinephrine (NE) or Noradrenaline (NA) (Levophed®)

About the Drug

- **Norepinephrine** [NOR-ep-i-NEF-rin] is a ***naturally*** **catecholamine.**
- *Secreted from* **adrenal medulla** ⇨ 20%.
- ***Act on*** **α-receptors *more than* β-receptors.**
- It is ***given*** **IV** for ***rapid*** **onset** of **action.**
- The ***duration of action*** is **1** to **2 minutes.**
- It is ***rapidly*** **metabolized** *by* **MAO** and **COMT**, and ***inactive*** **metabolites** are ***excreted*** in the **urine.**

CVS Actions

1) Vasoconstriction Effect:

- **Norepinephrine** causes ***greater*** **vasoconstriction** *effect than* **Epinephrine** (because it does not induce compensatory vasodilation via β_2 receptors on blood vessels supplying skeletal muscles).
- ↑ **Peripheral Resistance (PR)**; due to ***intense*** **vasoconstriction.**
- ↑ *both* **systolic** and **diastolic blood pressures.**

2) Baroreceptor Reflex:

- **Norepinephrine** ↑ **blood pressure** ⇨ ***stimulates*** **baroreceptors** ⇨ ↑ **vagal *activity*** ⇨ ***reflex*** **bradycardia.**
- ***Reflex*** **bradycardia** can ***blocked by*** **administration** *of* **Atropine** (blocks the transmission of vagal effects) ***before*** **Norepinephrine**.

Therapeutic Uses

- ***Used*** as a **Vasopressor** in ***treatment*** **Vasodilatory Shock** (acute severe hypotension such as in septic shock).
- It has ***no other*** **clinically *significant*** **uses**, *because* ***weak*** **β_2 activity** of **Norepinephrine**.

Side Effects

- **CNS effects: anxiety** and **headache.**
- **CVS effects: hypertension** and **reflex bradycardia.**
- **Local effects**: **Blanching** along the site of the infused vein (due to potent vasoconstrictor effects) with ↑ venous permeability ⇨ lead to extravasation (leakage of drug from the vessel into tissues surrounding the injection site) ⇨ lead to ***local*** **tissue necrosis** and *rarely* **tissue sloughing** (*treated by* **Phentolamine**).

Isoproterenol or Isoprenaline or Isopropyl noradrenaline (Isuprel®)

About the Drug

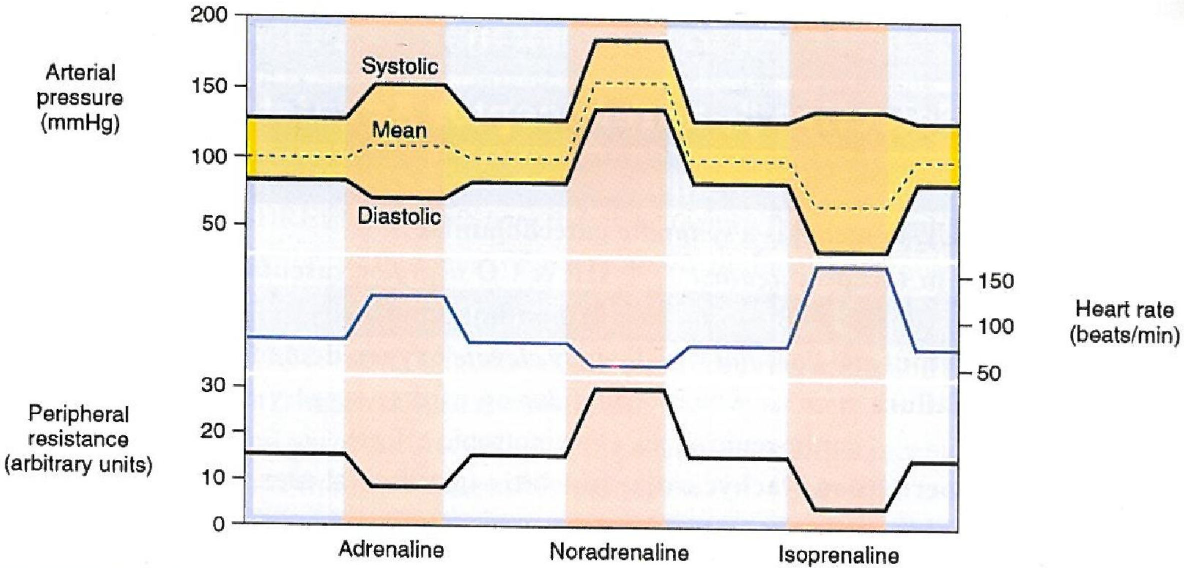
- **Isoproterenol** [eye-soe-proe-TER-e-nole] is a ***synthetic*** **catecholamine.**
- ***Stimulates both*** **β_1** and **β_2 receptors** (insignificant activity on α receptors).
- It is ***rarely*** **used therapeutically** *due to* **non-selectivity.**

Pharmacological Action

- **Heart** ⇨ ↑ **heart rate, force of contraction** and **cardiac output** ⇨ ***moderate*** ↑ **systolic pressure (β_1).**
- **Skeletal muscle** ⇨ **dilate arterioles** ⇨ ↓ **peripheral resistance** ⇨ ***marked*** ↓ **diastolic pressure (β_2).**
- **Bronchi** ⇨ ***potent*** **bronchodilator effect (β_2).**

Therapeutic Uses

- **Heart attack** and ***certain*** **types** of **irregular heartbeat (heart block).**
- **Acute attack** *of* **bronchial asthma.**
- *N.B:*
  - The ***use*** of **Isoproterenol** has ***largely*** *been* ***replaced*** *with* ***other*** **drugs.**
  - ***Side effects***: ***similar to*** those of **Epinephrine.**



Dopamine (DA) (Intropin®)

About the Drug

- **Dopamine** [DOE-pa-meen] is a ***naturally*** **catecholamine**.
- In the **brain**, **dopamine functions** as a ***neurotransmitter*** and ***plays*** a **number** of ***important*** **roles** *as well as* in the ***outside*** the **brain**.
- It is ***rapidly*** **metabolized** *by* **MAO** or **COMT**.
- It is can ***activate*** **α**- and **β-adrenergic receptors** *as well as* **dopaminergic *receptors***.

Dose-Dependent Effects

☞ In ***small*** **dose** ⇨ ***activate*** **D-dopaminergic *receptors***.
☞ In ***moderate*** **dose** ⇨ ***activate*** **β-adrenergic *receptors***.
☞ In ***high*** **dose** ⇨ ***activate*** **α-adrenergic *receptors***.

Pharmacological Action

- **Cardiac stimulatory effects:**
  - (+ve) **inotropic** and **chronotropic effects** ☞ **β_1**
- **Dilates renal blood vessels**:
  - ***Increase*** **blood flow** to the **kidneys** ☞ **D_1**
- **Vasoconstrictor effects** (*at very* **high doses**):
  - **Vasoconstriction** ☞ α_1

Therapeutic Uses

- **Cardiogenic** and **Septic Shock**: (by continuous infusion)
  - ☞ ↑ **blood pressure** {↑ CO (β_1) and ↑ PR (α_1)}.
  - ☞ ↑ ***perfusion*** to the **kidney** (D_1) ⇨ ↑ **glomerular filtration rate** ⇨ **diuresis**.
- **N.B**: First researchers suggest; the dopamine used as first-line choice for shock, (particularly septic shock), but recently; norepinephrine became the drug of first choice because; dopamine causes arrhythmia and has high mortality rate.
- **Hypotension** and **Severe Heart Failure**: ***primarily***
  - In patients with low or normal peripheral vascular resistance.
  - In patients who have oliguria (low urine output).

Side Effects

- **Tachycardia, hypertension, nausea, vomiting** and **headache**.

Dopexamine (Dopacard®)

About the Drug

- **Dopexamine** is a ***synthetic*** **analogue** of **Dopamine**, it ***stimulate*** **D_1 & β_1 receptors** (not dose dependant). It is ***rapidly*** **eliminated** *from* **blood**. ***Uses*** and ***side effects*** *same as* **Dopamine**.

Side Effects

- *Most* **adverse effects** are *mild* and tend to **diminish** with *continued* **therapy**.
- The *most frequent* **adverse effects** (dose-related) are:
  - **Dry mouth, drowsiness, dizziness, constipation** and **sedation**.
- The *less frequent* (rare) **adverse effects** are:
  - **Fatigue, headache, mental depression** and **Na^+** and **water retention**.
- **FDA pregnancy category C**

Withdrawal

- **Clonidine therapy** ***should be gradually*** **tapered** *off*.
- **Clonidine** *suppresses* **sympathetic outflow** *resulting* in *lower* **blood pressure**, ***but sudden*** **discontinuation** can cause ***rebound*** **hypertension** due to a rebound in sympathetic outflow.
- **Clonidine withdrawal hypertension** *treated by* **α_1** and **β blockers**.

α-Methyldopa (Aldomet®)

About the Drug

- **Methyldopa** [meth-ill-DOE-puh] is an **α_2 agonist** that has ***both*** **central** and **peripheral** *effects*.
- Its *primary* **clinical use** is as an **antihypertensive agent**.

Mechanism OF Action

[Methyldopa has a dual mechanism of action]

1) **Methyldopa** is *converted into* the ***false*** **transmitter** (metabolite) *called*; **alpha-methyl-norepinephrine**, in the **CNS** by **dopamine beta-hydroxylase (DBH) enzyme** ⇨ The ***false*** **transmitter** is *central* **α_2-agonist** ⇨ ↓ **sympathetic** *outflow* ⇨ ↓ **NE** *release* ⇨ ↓ **renin** *release* ⇨ ↓ **blood pressure**.

2) It is a *competitive* **inhibitor** *of* **dopa-decarboxylase** *enzyme* ⇨ *which converts* **L-dopa** *into* **Dopamine** ⇨ **Dopamine** is a ***precursor*** for **Norepinephrine** and *subsequently* **Epinephrine**.

Therapeutic Uses

- **Hypertension**.
- **Gestational hypertension** and **pre-eclampsia** (pregnancy-induced hypertension).
- **FDA pregnancy category B**
- **Used** with *caution* in **lactating women** (appears in breast milk).

Side Effects

☞ **Sympathetic blocked:**
- Postural hypotension, failure of ejaculation and nasal congestion.

☞ **CNS manifestation:**
- Sedation, drowsiness, depression and Parkinsonian symptoms.

☞ **Increase prolactin hormone:**
- Due to inhibition of dopaminergic mechanism ⇨ ↑ prolactin hormone
  - ⇨ **Gynecomastia** (breast enlargement) and **impotence** in ***male***, **galactorrhea** (Spontaneous flow of milk from the breast) and **amenorrhea** (absence of menstrual cycles) in ***female***.

☞ **Others** ⇨ May cause bone marrow depression and hepatotoxicity.

Clonidine Like Drugs

Guanfacine (Tenex®)

- **Guanfacine** [GWAHN-fa-seen] *used* in the *treatment of* **attention deficit hyperactivity disorder (ADHD)** and **hypertension**.

Guanabenz (Wytensin®)

- **Guanabenz** [GWAN-a-benz] an **antihypertensive agent**.

Apraclonidine (Iopidine®)

- **Apraclonidine** [app-rah-KLOE-nih-deen] is an **α_2 agonist** with ***weak*** **α_1 agonist** effects, ***used*** in **glaucoma *therapy*** (prevent intraocular pressure elevation).

Brimonidine (Alphagan®)

- **Brimonidine** [bri-MOE-ni-DEEN] is an **α_2 agonist**, ***used*** in **open-angle glaucoma** and **ocular hypertension** ☞ **α_2 agonist** ⇨ ↓ cAMP ⇨ ↓ aqueous humour production by the ciliary body.
- In 2013, the FDA approved ***topical*** application of **Brimonidine** 0.33% (Mirvaso®) for **facial erythema** or **rosacea** by ***narrowing*** **blood vessels**.

Lofexidine (Detoxydine®)

- **Lofexidine** [Lo-fex-ee-deen] is an **α_2 agonist**. It can be ***used*** as a short acting **anti-hypertensive**, but is ***mostly used*** to help ***relieve*** **symptoms** of **heroin** or **opiate *withdrawal*** in **opiate dependency**.

Selective Imidazoline Receptors Agonists

Rilmenidine (Hyperium®) | Moxonidine (Cynt®)

- ***Used*** in ***treatment of*** **hypertension**.

Selective β_2-adrenoceptor Agonists (BAA)

Mechanism OF Action

- ***In general*** activation of **β_2-adrenergic** receptors ☞
  - **Smooth muscles**; **Bronchodilatation** & **uterine muscle** *relaxation*.
  - **Skeletal Muscles**; **Vasodilatation *effect***.
  - **Mast cells**; ↓ ***release*** of **mediators** (*such as* **Histamine**) of ***immediate*** **hypersensitivity** from **mast cells**.
  - **Liver**; **glycogenolysis** (particularly if used in high doses).

Therapeutic Uses

- They are ***primarily*** **used** to ***treat*** **bronchial asthma** and other **pulmonary disorders** such as **Chronic Obstructive Pulmonary Disease (COPD)**.
- ***Other specified uses:***
  - **Ritodrine** **used** in ***control*** of **premature labor**.
  - **Salbutamol** may be **used** in ***treatment emergency*** **hyperkalemia**.

Routes OF Administration

- The choice of route of administration and drug to use depends on the desired clinical effect.
- Inhaled route produces at least as much bronchodilation as oral or parenteral therapy and does so with substantially fewer side effects.

Side Effects

- **Tachycardia (palpitations)**; especially in parenteral administration.
- **Tremor**; especially in oral and parenteral administration.
- **Insomnia**, **anxiety**, **dizziness**, **headache** and **nervousness**.

Short-acting β_2-adrenoceptor Agonists (SABA)

- **SABA**; **4-6 hours**.

Metaproterenol or Orciprenaline (Alupent®)

- **Metaproterenol** [met-a-proe-TER-e-nol] is a ***short acting*** **β_2 agonist**.
- It is **structurally** and **pharmacologically *similar*** to **Isoproterenol**.
- It is ***not*** **metabolized** by **Catechol-O-Methyltransferase (COMT)**.
- *Adult dose*
  - **Oral**: 20 mg 3 to 4 times a day.
  - **Inhalation aerosol**: 2 to 3 inhalations every 3 to 4 hours, up to 12 inhalations/day.

Salbutamol or Albuterol (Ventolin®)

- **Salbutamol** [sal-BYOU-tuh-mole] or **Albuterol** [al-BUE-ter-ol] is a ***short acting*** **β_2 agonist**.

Dose

- *Adult dose*:
  - **Oral**: 2 to 4 mg orally 3 to 4 times a day.
  - **Metered-dose inhaler**: 2 puffs every 4 to 6 hours.
  - **Inhalation capsules**: 200 mcg inhaled every 4 to 6 hours.

Therapeutic Uses

- **Therapeutic Uses**;
  - **Bronchospasm.**
  - **Chronic obstructive pulmonary disease (COPD).**
- **Other Uses**;
  - **Acute Hyperkalemia** (↑ K^+ to flow in cells thus ↓ level in the blood).
- **Off-Label Uses**: (Not approved by the FDA);

  But; **Clenbuterol** more preferred for this purposes ☞
  - **Bodybuilding** and **Animal Feeding:**
    - Fat burning (lipolysis) and muscle gain (protein synthesis).
  - **Doping**: ↑ performance in healthy athletes.

Terbutaline (Bricanyl®)

- **Terbutaline** [ter-BUE-ta-leen] is a ***short acting*** **β_2 agonist**.

Dose

- **Oral**: 2.5 to 5 mg 3 times daily.
- **SC:** 0.25 mg as a single dose, May repeat in 15 to 30 min. (max. 0.5 mg as a total dose in 4 h).

Therapeutic Uses

- **Therapeutic Uses**: **Bronchospasm.**
- **Off-Label Uses**: (Not approved by the FDA)
  - **Preterm Labor**:
    - Brethine® (**Terbutaline**) is *one* of the ***most*** **frequently used drugs** in the ***treatment*** of **preterm labor.**
    - **Subcutaneous dose** is 0.25 mg every 20 to 60 minutes until a woman's contractions have subsided.
    - **FDA warning** ☞ **Terbutaline** ***should not*** be **used** to *treat* **prolonged** (more than 48 to 72 hours) **premature labor.**
    - **FDA pregnancy category C.**
  - **Priapism** (***persistent*** **penile erection**):
    - **Oral Terbutaline** used in **patients** with ***prolonged*** **erections** of ***less than*** **4-hours** ***duration***, by relaxation of the stretched corporeal smooth muscles.

Levosalbutamol or Levalbuterol (Xopenex®)

- **Levosalbutamol** is the *R*-enantiomer of **Salbutamol**.
- ***Comparison to*** **Salbutamol**;
  - It has ***similar*** **therapeutic effects.**
  - ***No benefit*** of **Levosalbutamol** *compared to* **Salbutamol** (systematic review in 2013).

Pirbuterol (Maxair®)

- **Pirbuterol** [pir-BUE-ter-ol] is a ***short acting*** **β_2 agonist** ***used*** in **asthma** and **COPD.**

Ritodrine (Yutopar®)

- **Ritodrine** [RIT-oh-dreen] is a ***tocolytic drug***, ***used*** to ***stop*** **premature labor.**
- **FDA pregnancy Category B.**

Long-acting β2-adrenoceptor Agonists (LABA)

- **LABA**; **12 hours** (should not be used to treat acute symptoms).

Formoterol (Foradil®) | Salmeterol (Serevent®)

- **Formoterol** [for-MOE-ter-ol], **Salmeterol** [sal-MEE-ter-ol] are ***long acting*** **β2 agonist**.
- ***Duration of action:*** *extended up* to **12 hours**.

Therapeutic Uses

- ***Treatment*** of **Asthma**:
  - **LABA** **must** **be** **used** *in* **asthma** in ***combination with another long-term asthma-control medicine*** (e.g. **Inhaled Corticosteroids** such as **Fluticasone** and **Budesonide**).
    - Symbicort® ⇨ (**Budesonide** + **Formoterol**)
    - Advair® ⇨ (**Fluticasone** + **Salmeterol**)
- **Chronic Obstructive Pulmonary Disease** (**COPD**), *may* *be* used as ***mono-therapy*** or in ***combination*** with **corticosteroids**.
- ***Before*** **Exercise**:
  - **LABA** may be used ***before*** **exercise** to ***prevent*** **exercise-induced bronchospasm** (**EIB**).

FDA Warning

- **LABA** have been shown to ***increase*** the ***risk*** of **asthma-related death** in **pediatric** and **teenager patients**.

***** ASTHMA-RELATED DEATH *****

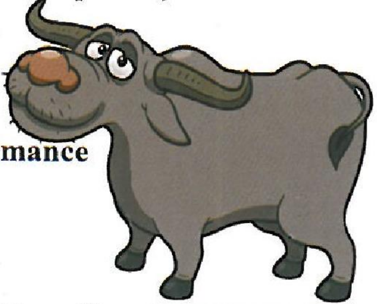
- **LABA** ***should*** ***not*** be **used** as a **mono-therapy** in the ***treatment*** of **asthma** to ***minimize*** **serious reactions** such as **asthma related deaths**.

Contra indication

- **Treatment** of **asthma** ***without*** **use** of a ***long-term*** **asthma control medication** *such as* an **inhaled corticosteroid**.

Clenbuterol (Spiropent®)

- **Clenbuterol** [clen-BYOO-ter-ol] is a ***long acting*** **β2 agonist**.
- ***Effect of*** **β2-adrenoceptor** ***agonists*** in **body** ***metabolism*** (**Clenbuterol more potent**) ☞
  - ↑ **Fat burning** (lipolysis) and ↑ **muscle gain** (protein synthesis).
- ***Human*** **Use**:
  - **Therapeutic Use** (*rare*): **Asthma** and **COPD**.
  - **Off-Label Uses**: **Bodybuilding**, **weight-loss** and **enhance performance** *in* **athletes**.



- ***Veterinary*** **Use**:
  - **Therapeutic Use**: as **Bronchodilator** in ***horses***.
  - **Animal Production**: **Clenbuterol** (Ventipulmin®), **Zilpaterol** (Zilmax®) and **Ractopamine** (Optaflexx®) are **β2-adrenergic** ***agonists*** *widely* **used** for ***increase*** the **size** of **animals** and the ***efficiency*** of **feeding** them.

Ultra-long-acting β2-adrenoceptor Agonists (Ultra-LABA)

- **Ultra-LABA**; **24 hours**.

Indacaterol (Onbrez®)

- **Indacaterol** [IN-da-KA-ter-ol] is an ***ultra-long acting*** **β2 agonist**.
- ***Indicated*** for ***long-term*** **control** *of* **chronic obstructive pulmonary disease** (**COPD**) ***symptoms***.
- **Used** ***once*** **daily** at the same time of day.
- **FDA warning** ☞ **Asthma-related death** (Contraindicated in patients with acute asthma without use inhaled corticosteroids).

Selective β_3-adrenoceptor Agonists

Mirabegron (Myrbetriq^{R})

- **Mirabegron** [MIR-a-BEG-ron] is a **β_3 agonist.**
- It is ***activate*** the **β_3 adrenergic receptor** in the **detrusor muscle** in the **bladder**, which *leads to* **muscle relaxation** and an ***increase*** in **bladder capacity.**
- ***It is used for*** patients with **Overactive Bladder (OAB).**
- ***Adverse effect*** ⇨ ***increase*** **blood pressure** and ***should not*** be **used** in **patients** with ***uncontrolled*** **hypertension.**

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2) Indirect-Acting Adrenergic Agonists

- **Indirect-acting adrenergic agonists** ☞
  - ***Increase*** **release** of **Epinephrine** or **Norepinephrine.**
  - ***Inhibit*** the **reuptake** of **Epinephrine** or **Norepinephrine.**
  - ***Inhibit*** the **degradation** of **Epinephrine** or **Norepinephrine.**
- ***Not*** **directly** ***affect*** **postsynaptic receptors.**

Amphetamine (Adderall^{R})

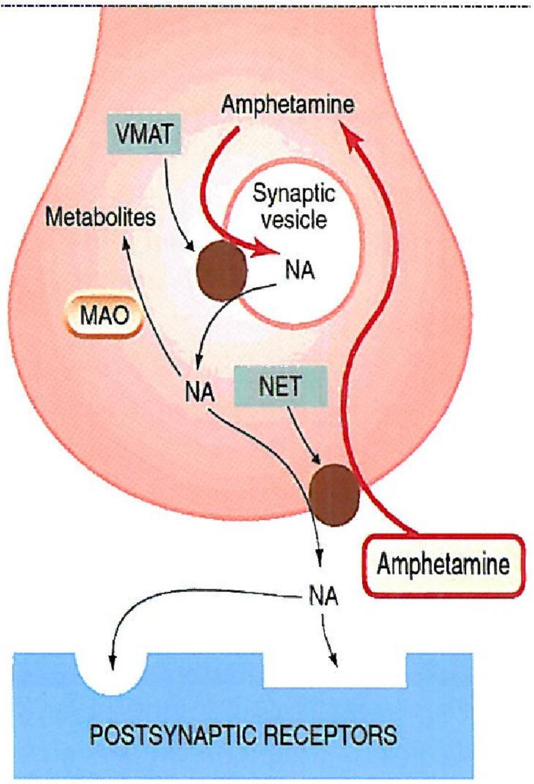
About the Drug

- **Amphetamine** [am-FET-a-meen] is a ***potent*** **CNS stimulant.**
- It is a ***racemic mixture*** of **Phenyl-isopropyl-amine.**
- It is *readily* ***enters*** the **CNS** ⇨ marked ***stimulant effects*** on **mood** and **alertness** and a ***depressant effect*** on **appetite.**
- It is has a **mood-elevating (*euphoria*) effect**, this effect is the basis for widespread ***abuse*** of this **drug**.
- It is **D-isomer** is ***more*** **potent** ***than*** **L-isomer.**

Amphetamines

Mechanism OF Action

- **Amphetamine** and **amphetamine-like drugs** are ***non-catecholamine*** **sympathomimetic amines** *with* **CNS stimulant** ***activity***.
- **Amphetamines** ***enters*** the **nerve terminal** *via* the **norepinephrine transporter (NET)** and ***enters*** **synaptic vesicles** *via* the **vesicular monoamine transporter (VMAT)**, in ***exchange*** *for* **noradrenaline** (***displace*** *stored* **NA**), which ***escapes*** *into* the **cytosol**.
- **Amphetamines** also ***reduces*** **NA** ***reuptake*** *via* the **transporter**.



Amphetamines increase release and decrease reuptake of monoamines (NE and Dopamine)

Pharmacological Action

- *Indirect* **sympathomimetic effects** of **amphetamines** ⇨ ***stimulate*** *both* **α** and **β receptors**.
- It ***causes*** **VC**, **↑ HR** and **↑ CO** ⇨ lead to ***modest* ↑ *in* blood pressure**.

- Due to ***increases*** **central Dopamine** and **Norepinephrine** ⇨ *causing* **wakefulness** and **euphoria**.
- ***Stimulate*** **cerebrospinal axis, cortex, brain stem** and **medulla** ⇨ ***increase*** **alertness** and ***decrease*** **fatigue**.
- ***Stimulate*** **respiratory center** (**RC**) ⇨ *producing* ***faster*** and ***deeper*** **breaths**.
- ***Slight*** **analgesic** ***effect***.
- **Anorexigenic** ***effect*** (loss of appetite).

- ***Contraction*** in the **urinary bladder** *sphincter* ⇨ ***difficulty*** **urination**.
- The effects of **Amphetamine** on the **GIT** are *unpredictable* (***diarrhea*** or ***constipation***).

Therapeutic Uses

- **Attention Deficit Hyperactivity Disorder (ADHD)**:

  - **ADHD**; implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years.
  - Children with ADHD may produce weak dopamine signals in the brain.
  - **Amphetamines** may help to increase the ability to pay attention, concentrate, stay focused, and stop fidgeting.

- **Narcolepsy** (**Chronic Sleep Disorder**):

  - **Narcolepsy;** is a chronic neurological disorder involving the loss of the brain ability to regulate sleep-wake cycles normally.
  - **Amphetamines** helps to stay awake during the day. It should not be used to treat tiredness or to hold off sleep in people who do not have a sleep disorder.

- ***Off-label*** **uses**:
  - **Performance-enhancing**;
    - Improve overall work performance.
  - **Treatment of Depression**;
    - Usually in conjunction with a standard antidepressant drug.
  - **Obesity Treatment**;
    - Due to anorexigenic effect.

Side Effects

☞ **Cardiovascular** *side effects*:

- **Palpitations (tachycardia)** and *increase* **blood pressure**.

☞ **CNS** *side effects*:

- **Insomnia, anxiety, confusion, hallucination** and **tremor**.

☞ **Other** *side effects*:

- **Weight loss, bladder pain** (painful urination), **headache, nausea, vomiting, abdominal cramps** and **diarrhea** or **constipation**.

Contra indication

- **Patients** *with;* **Cardiovascular diseases, advanced arteriosclerosis, hyperthyroidism,** *severe* **agitation** or *severe* **anxiety** and **glaucoma**.
- **Patients** *with* a **history** of **drug abuse** or those *taking* **MAO inhibitors**.

FDA Warning

- *Administration* of **Amphetamines** for ***prolonged*** **periods** of time *may lead to* **drug dependence**, and, therefore, this must be avoided.

**** AMPHETAMINES-RELATED DEATH ****

- ***Misuse*** of **Amphetamines** *may cause* ***sudden*** **death** and ***serious*** **cardiovascular adverse events** (heart attack and heart stroke).

Amphetamine Derivatives

Dextroamphetamine (Dexedrine®) | Lisdexamfetamine (Vyvanse®)

- **Dextroamphetamine** [DEX-troe-am-FET-a-meen] is the ***more*** **active** (dextrorotatory) ***enantiomer*** of the **Amphetamine** molecule.
- **Lisdexamfetamine** [lis-dex-am-FET-a-meen] is a ***prodrug*** that is ***converted to*** the ***active*** **component Dextroamphetamine** ***after*** **GI** ***absorption*** and ***metabolism***.
- The **pharmacological effects** and **therapeutic uses** of **Dextroamphetamine** *like* **Amphetamine**.

Methamphetamine (Desoxyn®)

- **Methamphetamine** [meth-am-FETa-meen] also known as "**speed**".
- It is *like* **Amphetamine** ***but***; ***much*** **stronger**, *act* **quicker**, and can be *considered* ***more*** **addicting**.
- ***Therapeutic Uses***: ***approved*** *by the* **FDA** ***for treating*** ☞
  - **Attention Deficit Hyperactivity Disorder (ADHD)**.
  - **Exogenous obesity**: obesity originating from factors outside the patient's control.
- ***Off-Label Uses***: ***Increase*** **sexual desire**, ***lift*** the **mood**, ***increase*** **energy, depression** & **narcolepsy**.

Methylphenidate (Ritalin®)

- **Methylphenidate** [meth-ill-FEN-ih-date] is an **amphetamine derivatives** with ***less*** **side effects**.
- **Addiction** and **psychological dependence** are ***rare*** with **Methylphenidate**.
- It is presently **one** of the ***most prescribed*** **medications** in **ADHD**.
- It is also ***effective*** in the **treatment** of **narcolepsy**.
- ***Off-label uses***: **Depression** and **performance-*enhancing***.

Modafinil (Provigil®)

- **Modafinil** [moe-DAF-i-nil] is a ***wakefulness-promoting agent***.
- ***Uses***: **sleep disorders; narcolepsy, obstructive sleep apnea (OSA),** and **shift work disorder (SWD)**. The ***exact*** **mechanism** which **Modafinil** ***promotes*** **wakefulness** is *unknown*.
- In the **US military**, **Modafinil** has been **used** on certain **Air Force missions** as a "**go pill**".

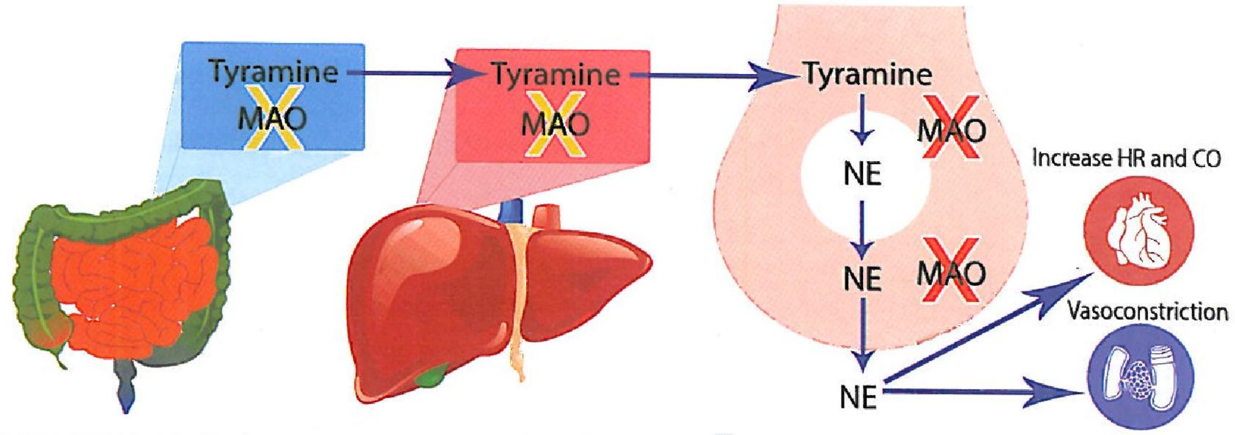
Fenethylline (Captagon®)

- **Fenethylline** is a ***prodrug***, it is ***metabolized*** to form **2 drugs Amphetamine** and **Theophylline**.
- ***Most*** of the **Amphetamines** ***abused*** in **Saudi Arabia** and *other* **Arab countries** *come* in the form of **Captagon tablets**.

Other Indirect-Acting Adrenergic Agonists

Tyramine

- **Tyramine** [TIE-ra-meen] is a normal ***by-product*** of **tyrosine metabolism** and ***not a clinically used***.
- It is **important** because it is ***found in*** **fermented foods**, such as **aged cheese** (**ripe cheese**).
- ***Like* Amphetamines**, **Tyramine** can ***enter*** the **nerve terminal** and ***displace*** *stored* **Norepinephrine**.
- It is ***metabolized*** by **MAO** in the **GIT** and **liver**, *but*, **if the patient is taking MAO inhibitors**, **Tyramine** is ***not*** **metabolized**, as well as **NE** ***is not*** **metabolized** ⇨ ***powerful*** ↑ in **NE** ***release*** *from* **nerve ending** ⇨ ***serious*** **vasopressor effects** ☞ **Hypertensive crisis** (***treated*** *by* **α_1** and **β blockers**).



Cocaine

- **Cocaine** [koe-KANE] is a ***powerful*** **CNS stimulant**.
- It is acts as a **Serotonin–Norepinephrine–Dopamine** **reuptake** ***inhibitor***, also known as a **Triple Reuptake Inhibitors** (**TRI**).
- It is a **local anesthetic** ⇨ **sodium channel blocker** ⇨ *produce* **anaesthesia**.
- ***Like* Amphetamines**, it can ***increase*** **blood pressure** by ***indirect*** **mechanism**.
- **Cocaine** as a **drug of abuse** is *discussed* in *CNS chapter*.

3) Mixed-Acting Adrenergic Agonists

Ephedrine (Ephedrine sulfate®)

About the Drug

- **Ephedrine** [eh-FED-rin] is a ***natural*** **alkaloid** *found in* various **plants** in the genus ***Ephedra***.
- It has been used in China for over 2000 years and it was introduced into medicine in 1924 as the ***first*** **orally** ***active*** **sympathomimetic drug**.
- It is ***not*** a **catechol** ⇨ ***resist*** **MAO** and **COMT** ⇨ ***long*** **duration**.
- It is ***similar in*** **structure** to the **Amphetamine derivatives**.
- ***Excellent*** **absorption orally** and ***penetrate*** into the **CNS**.

Mechanism OF Action

- **Direct** and **indirect** actions (**mixed-action**) on the adrenergic receptors.
- **Direct**: Ephedrine increases post-synaptic noradrenergic receptor activity by activate post-synaptic α-receptors and β-receptors. (***Weakly***).
- **Indirect**: **Amphetamine like action**; Ephedrine increase release of stored norepinephrine from synaptic vesicles.

Pharmacological Action

- *Increase* **systolic** and **diastolic blood pressures** by **vasoconstriction** (α_1) and **cardiac stimulation** (β_1).
- ***Mild*** **CNS stimulation ⇨ ↑ alertness, ↓ fatigue** and ***prevents*** **sleep** (improves athletic performance).
- **Bronchodilation**, but it is ***less*** **potent** and ***slower*** **acting** *than* **Epinephrine**.
- **Decongestant effect** (due to vasoconstriction).

Therapeutic Uses

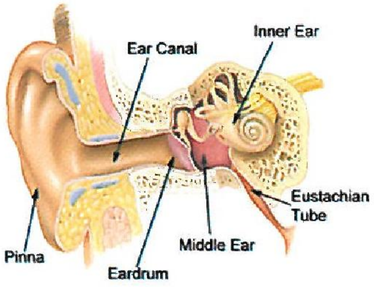
- -- **Hypotension** *associated with* **anaesthesia.**
- -- **Nasal congestion** (due to nasal decongestant effect).
- Relieve acute bronchospasm, but it is less effective than epinephrine.
- As a stimulant or concentration aid (Performance-enhancing).
- Appetite suppressant.

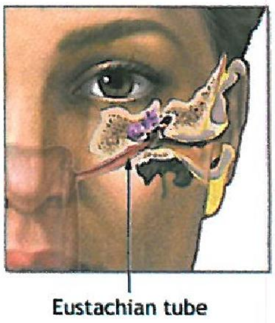
Side Effects

- **Palpitation.**
- **Headache.**
- **Insomnia** and **hyperactivity**.
- **Nausea** or **vomiting**.

Pseudoephedrine (Sudafed®)

- **Pseudoephedrine** [SOO-doe-eh-FED-rin] is a ***diastereomer*** of **Ephedrine.**
- It has ***fewer*** **CNS** and **CVS** ***side effects than*** **Ephedrine.**
- It **used** ***widely*** as a ***combination*** to *relieve* **common cold symptoms**. (Actifed®)
- *Uses*:
    - **Nasal congestion.**
    - **Sinus congestion.**
    - **Eustachian tube congestion.**
- It has been **illegally used** to **produce methamphetamine** (illicit manufacture), ***Therefore***, products containing pseudoephedrine have certain restrictions in some countries.
- *Contraindicated* in: *severe* **hypertension, Pregnancy (Category C)** and **breast-feeding mothers**.
- **Eustachian** [yoo-STAY-shun] **tube:** is a tube that links the nasopharynx to the middle ear.
- ***Function***:
    - Equalizing pressure between the middle ear and the atmosphere
    - Drains mucus from the middle ear.
- Otitis media, or inflammation of the middle ear, commonly affects the Eustachian tube (congestion).





B: Adrenergic Antagonists (Adrenergic Blockers)

1) α-adrenoceptor Antagonists (α-adrenergic Blockers)

A: Non-Selective α-adrenoceptor Antagonists

Irreversible Non-Competitive

Phenoxybenzamine (Dibenzyline®)

- **Phenoxybenzamine** [fen-OX-ee-BEN-za-meen] is a **non-selective** ***irreversible non-competitive*** **α-adrenoceptor** *antagonist*.
- It is **binds** ***covalently*** to both α_1 and α_2 **receptors** and the ***only*** way the **body** can **overcome the block**; is to ***synthesize*** *new* **α-adrenoceptors**, which *requires* a **day** or ***longer***.
- ***Covalent*** **binding** with the **receptors** ***due to*** *presence* of **N-chloro-ethyl** group.
- *Half-life*: **about 24 hours**. (long acting)
- *Duration of action*: 3 to 4 days.
- *Routes of administration*: Orally.

Reversible Competitive

Tolazoline (Priscoline®) | **Phentolamine** (Rogitine®)

- **Tolazoline** [tol-A-zoe-lin] and **Phentolamine** [fen-TOL-a-meen] are **non-selective** ***reversible competitive*** **α-adrenoceptor** ***antagonist***.
- They are a ***competitive*** **block** of α_1 and α_2 **receptors**.
- **Phentolamine** ***more*** **potent** than **Tolazoline**.
- *Duration of action*: *approximately* **4 hours** ***after*** a **single** ***injection*** (short acting).
- *Routes of administration*: ***Parenterally***.

Pharmacological Action

- α_1 ***receptor blocker effect:***
  - Prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines ⇨ ↓ ***peripheral resistance*** ⇨ ↓ ***blood pressure*** ⇨ ***reflex tachycardia***.
- α_2 ***receptor blocker effect:***
  - Block presynaptic inhibitory α_2 receptors in the heart ⇨ ↑ NE release ⇨ stimulates β_1 receptors on the heart ⇨ ↑ CO.

Therapeutic Uses

A) Hypertension in **patients** *with* **pheochromocytoma**.

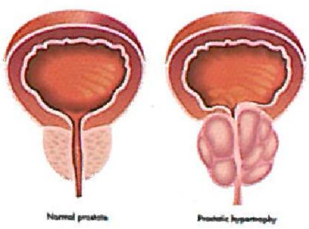
B) *Non-specific uses of non-selective α blockers:*

1) ***Symptomatic*** **Benign** (non-cancerous) **Prostatic Hyperplasia (BPH)**:

- Urinary retention associated with BPH treated by α-blockers which cause ⇨ relaxation of smooth muscle in the bladder neck, prostate, and prostate capsule ⇨ Improve urine outflow.

2) Raynaud's [RAY-nadds] **phenomenon**:

- Is a recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure.



Therapeutic Uses

3) Impotence (Erectile Dysfunction; ED):

- ***Side effects*** of intra-penile injections of non-selective α-blockers ⇨ **priapism** (painful prolonged erection lasting 4 hours or more), **fibrotic reaction** in **penis tissues** and **failure of ejaculation.**

C) **Phentolamine** used in ***prevention*** or ***treatment of*** **dermal necrosis** (caused by following IV extravasation of NE).

D) **Phentolamine** used in ***diagnosis*** of **pheochromocytoma (Phentolamine Blocking Test).**

E) **OraVerse®** (**Phentolamine**) injection; *is the* ***only*** **local anesthetic** ***reversal agent***. In 2008 FDA has approved OraVerse® for the reversal of soft-tissue anesthesia and the associated functional deficits resulting from a local dental anesthetic (about 55 min. vs. 155 min.).

Side Effects

- **Postural hypotension.**
- **Reflex tachycardia.**
- **Failure (difficulty) of ejaculation or retrograde ejaculation** ⇨ due to blocking α receptor in smooth muscles of vas deferens and ejaculatory ducts ⇨ failure of contraction.

B: Selective α_1-adrenoceptor Antagonists

Prazosin (Minipress®)

About the Drug

- **Prazosin** [PRAY-zoe-sin] is a **selective** ***competitive*** **α_1 receptors** ***blocker***.
- In contrast to non-selective α_1-adrenoceptor blockers, produce ***less reflex*** **tachycardia.**
- It acts by blocking postsynaptic α_1-adrenoceptors on vascular smooth muscle ⇨ vasodilatation ⇨ ↓ ***total*** **peripheral resistance** ⇨ ↓ **BP.**
- ***Routes of administration***: **Orally.**

Therapeutic Uses

- ***Treatment of*** **hypertension.**
- ***Symptomatic*** **Benign Prostatic Hyperplasia (BPH).**
- **Congestive Heart Failure (CHF):**
  - **Used** as an ***adjunct*** to **Digoxin** & **Diuretics** for the ***treatment*** of **CHF.**
  - *Due to* ↓ ***systemic*** **resistance** ⇨ ↓ ***preload*** and ***afterload*** ⇨ ↑ **CO.**
- **Pheochromocytoma:**
  - **Used *alone*** or in ***combination*** with **β-blockers.**
- **Peripheral vasospasm** *caused by* **ergot alkaloid** ***toxicity.***
- **Raynaud's phenomenon.**

Side Effects

- ***First-dose*** **orthostatic hypotension** (***initial*** **syncope attack** or ***first-dose*** **phenomenon)** ⇨ to ***overcome***; the **first dose** ***must*** *be* ***minimized*** and ***giving*** at **bed time.**
- Headache, dizziness, drowsiness and nausea.
- Edema (sodium and water retention).
- Priapism and failure of ejaculation (rare).

Doxazosin (Cardura®)	**Terazosin** (Hytrin®)

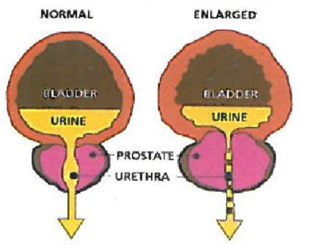
- **Doxazosin** [dox-AY-zoe-sin] and **Terazosin** [ter-AY-zoe-sin] are **selective** ***competitive*** **α_1 receptors** ***blockers used*** **Orally** ***for***: **symptoms** ***of*** **BPH** and **treatment** ***of*** **hypertension.**
- ***Side effects***: same as **Prazosin.**

Alfuzosin (Xatral®)

- **Alfuzosin** [al-FYOO-zoe-sin] is a ***selective*** **α_1 blocker** ***used*** *for* **symptoms** *of* **benign prostatic hyperplasia (BPH)**. ***Not used*** for the ***treatment*** of **hypertension**.
- **Alfuzosin** have ***better*** **cardiovascular tolerability** than **Prazosin**, **Terazosin** or **Doxazosin**.
- ***Most common side effects***: **dizziness, upper respiratory tract infection, headache** and **fatigue**.
- ***Contraindication***: patients with **renal insufficiency** and patients with history of **QT prolongation**.

Tamsulosin (Omnic Ocas®)

- **Tamsulosin** [tam-SUE-loh-sin] is a ***selective*** **α_1 blocker** that has ***preferential*** **selectivity** for the **α_{1A} receptor** in the **prostate** *versus* the **α_{1B} receptor** in the **blood vessels**.
- **Tamsulosin** is the ***most drug prescribed*** (***more selective***) in ***symptoms of*** **benign prostatic hyperplasia (BPH)**.
- It has some benefit in ***allowing*** **kidney stones** to *pass through* the **ureter**.



- ***Dosage form***:
    - **Tamsulosin MR** (Modified Release) capsule.
    - **Tamsulosin OCAS** (Oral-Controlled Absorption System) cap.
    - **Tamsulosin OCAS** appeared to have the ***most favourable*** **efficacy/tolerability ratio**.
- ***Dose***: **Initial Dose**: 0.4 mg orally once a day - **Maximum Dose**: 0.8 mg orally once a day.
- ***Most common side effect***: **Failure of ejaculation or retrograde ejaculation**.

Silodosin (Rapaflo®)

- **Silodosin** [SIL-oh-DOE-sin] is a selective α_1 blocker (selective **α_{1A} receptor**) in the prostate.
- It is used in ***symptoms of*** **benign prostatic hyperplasia (BPH)**.
- ***Same as*** **Tamsulosin** *but* **Silodosin** acts ***more*** **rapidly**.

Other Drugs Used in BPH (Not Act on α_1 Receptors)

Finasteride (Proscar®)

Dutasteride (Avodart®)

- **Finasteride** [fin-AS-ter-ide] and **Dutasteride** [doo-TAS-ter-ide] are a **5α-reductase *inhibitors***.
- They are ***inhibits 5α-reductase enzyme*** which convert **testosterone** into the ***more potent androgen*** **dihydrotestosterone** this lead to **reduction** *in* **prostate *size*** with ***improve* in urinary *flow***.
- ***Used*** primarily in the treatment of **benign prostatic hyperplasia (BPH)** and **androgenic alopecia**.
- ***Side effects***: ↑ **risk of impotence** (5%), ↓ **sexual desire** (3%) and **failure of ejaculation** (1%).
- **Duodart®** (**Dutasteride** 0.5 mg + **Tamsulosin** 0.4 mg) is a ***combination*** used ***once*** **daily** in **BPH**.

Tadalafil (Cialis®)

- Approved for treatment of **erectile dysfunction**, **symptoms** *of* **benign prostatic hyperplasia (BPH)** or **combined erectile dysfunction** and ***symptoms of*** **BPH**. (discussed in ***next topic***) ☞

C: Selective α_2-adrenoceptor Antagonists

Yohimbine (Yohimbex®)

- **Yohimbine** [yoh-HIM-bean] is a **selective *competitive* α_2-blocker**.
- It is a ***natural alkaloid*** derived from the bark of the ***yohimbe*** tree in Central Africa.
- ***Uses***: **mydriatic**, **erectile dysfunction** and as **fat burner** (***promoting*** lipolysis; Lipo 6®).
- ***Mechanism of action***: The exact mechanism for its use in impotence has not been fully elucidated.
    - Yohimbine blocks central pre-synaptic α_2-adrenergic receptors ⇨ leads to ↑ release of neurotransmitters in CNS and in corpora cavernosum penis such as nitric oxide (NO), noradrenaline, and dopamine.
- ***Common side effects***: Tachycardia, hypertension, increased motor activity, tremor, and dizziness.

Other Drugs Used in Erectile Dysfunction (Not act on α_2 Receptors)

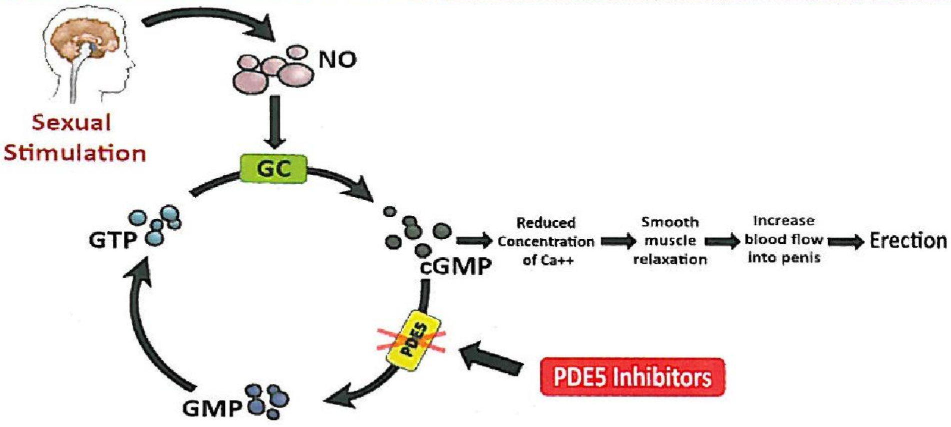
A) Phosphodiesterase Type-5 (PDE5) Inhibitors

Sildenafil (Viagra®)

About the Drug

- **Sildenafil** [sil-DEN-a-fil] is a **Phosphodiesterase Type-5 (PDE5) Inhibitor**.
- **Early 1990s**: Pfizer completes several early trials of sildenafil citrate for its use as a heart disease treatment. But volunteers in the clinical trials are reporting increased erections several days after taking a dose of the drug.
- **In 1998** the FDA approved Viagra® (**Blue pill**) to treat erectile dysfunction (ED) and *pulmonary arterial hypertension* (PAH).

Mechanism OF Action



- ***During*** **sexual stimulation** ⇨ ***stimulate*** **release** of **nitric oxide (NO)** in the **corpus cavernosum** in the **penis**.
- **NO** ***release*** ⇨ ***activate*** **guanylate cyclase** (GC) ⇨ ↑ **cyclic guanosine monophosphate** (cGMP) ⇨ ↓ **Ca^{2+}** ***influx*** ⇨ ***relaxation*** of **blood vessels smooth muscle** ⇨ **vasodilatation** ☞ **Erection**.
- **Phosphodiesterase type-5** *responsible for degradation* of **cGMP** *into* **GMP**.
- **Sildenafil** is a ***selective*** **phosphodiesterase type-5 (PDE5) inhibitor** ⇨ ***accumulation*** of **cGMP** ☞ **Erection**.
- **Sildenafil** has ***no effect*** in ***absence*** of **sexual** ***stimulation***.

Phosphodiesterase Enzymes

- **PDE enzyme** ***types***: PDE-1, 2, 3, 4, 5, 6, 7, 8, 9, 10 & 11.

Type	Main Function and Location
PDE-3	- Control cardiac contractility.
PDE-5	- Control contractility of pulmonary vascular smooth muscle and the corpus cavernosum.
PDE-6	- Control photo-transduction pathway of the retina.

- **Sildenafil** effect is more potent on PDE-5 than other phosphodiesterases.
    - The approximately 4,000 fold selectivity for PDE-5 versus PDE-3.
    - The approximately 10 fold selectivity for PDE-5 versus PDE-6.

Pharmaco Kinetics

- ***Absorption*** and ***Distribution***:
    - It is ***rapidly*** **absorbed** (orally).
    - ***Maximum*** **plasma concentrations** are ***reached*** *within* 30-120 minutes.
- ***Metabolism*** and ***Excretion***:
    - It is **metabolized** *predominantly by* **CYP450 (CYP3A4) hepatic microsomal** ***isoenzymes***.
    - It is ***excreted*** *predominantly* in the **feces** (80%) and in the **urine** (13%).

Therapeutic Uses

- **Treatment** *of* **erectile dysfunction (ED).**
- **Treatment** *of* **pulmonary arterial hypertension (PAH):**
  - It relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure.
- **Sildenafil 20 mg** can ***improve*** **fetoplacental perfusion** in **pregnancies.**
- N.B; ***vaginal*** Sildenafil may be ***effective*** for ***improving*** **uterine artery blood *flow*** and **endometrial development** in **IVF** (in vitro fertilization).

Dose

- ***Usual*** **Adult Dose** *for* **Pulmonary Hypertension:**
  - 20 mg orally three times a day.
- ***Usual*** **Adult Dose** *for* **Erectile Dysfunction:**
  - 50-100 mg orally once a day, as needed, 1 hour prior to sexual activity.
- ***Dose Adjustments*** **(Erectile Dysfunction):**
  - **Geriatric:** 25 mg 1 hour prior to sexual activity.
  - ***Mild to moderate*** **renal dysfunction:** No adjustment recommended.
  - ***Severe*** **renal dysfunction** (CrCl less than 30 mL/min): 25 mg.
  - **Hepatic impairment** (any degree): 25 mg.
  - With **alpha blockers** or with **CYP450 3A4 inhibitors** (ketoconazole or erythromycin): 25 mg.

Side Effects

- ***Most common*** **adverse effects:**
  - Headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness and rash.
  - **Abnormal vision:** due to inhibition of PDE-6.

**** In Details ****

- ***Common:*** (10% or more):
  - Headache (28%) dyspepsia (17%), abnormal vision (11%) {green vision/blue vision}
  - Diarrhea (10%), myalgia/back pain (10%), flushing (10%), nasal congestion (10%) and rash (10%).
- ***Uncommon*** (0.1% to 1%):
  - Tachycardia and hypotension ⇨ transient decreases in supine blood pressure in healthy volunteers (maximum decrease of 8.4/5.5 mmHg).

Contra indication

- In **patients** *who taking* **Organic Nitrites** and **Nitrates.**
- ***Severe*** **hepatic *impairment*** or ***severe*** **renal *impairment*.**
- **Hypotension,** ***recent*** **stroke** or **heart attack.**
- **Retinal disorders** (genetic disorders of retinal phosphodiesterases).

FDA Warning

- **Patients *should* stop Sildenafil** if a **sudden *loss of* vision occurs** in ***one*** or ***both*** **eyes,** *which* could be a ***sign*** of **Non Arteritic Anterior Ischemic Optic Neuropathy (NAION).**
- **Patients *should* stop Sildenafil** in the *event* of **sudden *decrease*** or ***loss of*** **hearing.**

Vardenafil (Levitra®) | Tadalafil (Cialis®)

- **Vardenafil** [var-DEN-a-fil] and **Tadalafil** [ta-DAL-a-fil] are ***selective*** **PDE-5 inhibitors used** *for* **erectile dysfunction.**
- Structurally **Vardenafil** is similar to **Sildenafil**, while **Tadalafil** is very different.
- **Vardenafil** is may be effective in the treatment of premature ejaculation!!
- **Tadalafil** used for in **treatment** *of* **pulmonary arterial hypertension** and **symptoms** *of* **benign prostatic hyperplasia (BPH).**
- **Vardenafil** is ***more*** **selective** *than* **Sildenafil** and **Tadalafil** to **PDE-5.**

- ***Brief comparison***:

	Sildenafil	Vardenafil	Tadalafil
FDA approval date	March 27, 1998	August 19, 2003	November 21, 2003
Dosage form	25mg, 50mg, 100mg tablets	2.5mg, 5mg, 10mg, 20mg tablets	5mg, 10mg, 20mg tablets
Efficacy	82-84%	80%	81%
Onset of action	30 minutes (effect delayed by food)	25 minutes (effect delayed by fatty meal)	16-45 minutes (effect NOT delayed by food)
Recommended dose	50 mg, may be adjusted to 100 mg or 25 mg	10 mg, may be adjusted to 20 mg	10 mg, may be adjusted to 20 mg
Duration of action	4 to 5 hours	4 to 5 hours	36 hours
Food Interactions	- Less effective after high-fat meal	- Less effective after high-fat meal - Moderate-fat meal does not reduce its effectiveness	- Works without regard to what eat
Most common side effects	Facial flushing, headache, indigestion	Facial flushing, headache	Headache, indigestion
Less common side effects	Altered vision, dizziness, nasal congestion	Indigestion, nausea, dizziness, nasal congestion	Back pain, muscle aches, nasal congestion, facial flushing, dizziness

Vardenafil is ***also available*** in an **orally disintegrating tablet** (**ODT**) *formulation*; ***not*** **affected** by a **high-fat meal**.

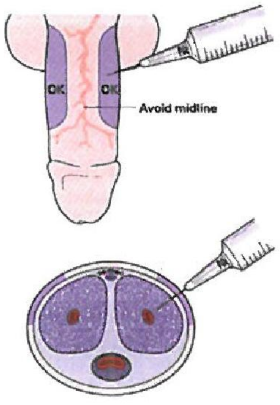
Avanafil (Stendra®)

- **Avanafil** [a-VAN-a-fil] is a ***selective*** **PDE5 inhibitor** ***approved*** for **erectile dysfunction** by **FDA** on **April 27, 2012**.
- ***Onset of action***: **15 minutes** (***Fast*** **onset** *of* **action**).
- ***Duration of action***: *up to* **6 hours**.
- ***Dosage form***: Tablets: 50, 100 and 200 mg.
- ***Side effects*** *same as* **Sildenafil**.

B) Prostaglandin E₁ analogue

Alprostadil (Caverject®)

☞ To understand what **prostaglandins** meaning; *see* Autacoids chapter (*next* chapter) (*See page* 107).



- **Alprostadil** [al-PROS-ta-dil] is a **prostaglandin E_1 (PGE_1)** ***analogue*** used in the ***continuous*** **treatment** of **erectile dysfunction** *due to* **vasodilatation** ***properties***.
- ***Dosage form***: **urethral suppositories** and in **injectable form**.
  - Penile suppository ***inserted*** into the **urethra**.
  - Injected by syringe ***directly*** into the **corpus cavernosum** of the **penis**.
- ***Onset of action***: 5 to 10 minutes.
- ***Duration of action***: Injection ⇨ 1 to 3 hours, supp.⇨ 30 to 60 minutes.
- ***Most common side effects***: pain at place of injection or pain of urethra (suppository only) and painful erection.

C) Other

Papaverine (Papacon®)

- **Papaverine** [pa-PAV-er-een] is an **opium alkaloid** ***antispasmodic drug***, used *primarily* in the treatment of **visceral spasm**, **vasospasm** and in the ***treatment of*** **erectile dysfunction**.

2) β-adrenoceptor Antagonists (Beta Blockers)

A: Non-selective β-adrenoceptor Antagonists

Propranolol (Inderal®)

About the Drug

- **Propranolol** [proe-PRAN-oh-lole] is a ***non-selective* beta blocker** drug.
- It **blocks** both β_1 and β_2 receptors with **equal affinity**.
- *James Whyte Black* (Scottish pharmacologist) successfully developed **propranolol** in 1960s. In 1988, he was awarded the Nobel Prize for this discovery.

Pharmaco Kinetics

- It is a ***highly* lipophilic** ⇨ readily crosses the blood–brain barrier (BBB) and the placenta and is distributed into breast milk.
- It is **almost *completely* absorbed** *after* **oral administration**.
- ***First-pass* effect**: ***only** about* **25%** of an **orally administered dose** *reaches* the **circulation**.
- ***Volume of distribution*** **(V_d)** of propranolol is quite large = 4 L/kg.
- It is ***extensively* metabolized**, most metabolites are ***excreted*** in the **urine**.

Pharmacological Action

- **(-ve) Inotropic** (Force) & **(-ve) Chronotropic** (HR).
- **Slow SA** (sinoatrial) and **AV** (atrioventricular) **nodal conduction**.
- ***Decrease* cardiac work** and **O_2 *consuming*** ⇨ useful in treatment of **angina**.

- ***Blocking* β_2-receptors** on the **skeletal muscle** ⇨ ***block* vasodilation effect**.
- ***Reflex* peripheral vasoconstriction**: **↓ CO ⇨ ↓ BP**, which triggers a reflex peripheral VC, ***but***; ***chronic* drug administration** *lead to* ***returns*** to ***normal*** or ***decreases*** **total peripheral resistance**.

- **Bronchoconstriction**: ***blocking* β_2 receptors** in the **lungs** of ***susceptible* patients** *causes* ***contraction*** of the **bronchiolar smooth muscle**.
- ***Non-selective* β-blockers** are ***contraindicated*** in **patients** with **COPD** or **asthma**.

- **β-blocking agents *reduce* intraocular pressure** (IOP) *especially* in **glaucoma** due to ***decrease* aqueous humour *formation***.

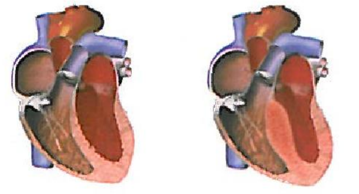
Metabolic Effects

- ***Block* β-receptors** in the **adipose tissues** ⇨ **↓ Lipolysis**.
- ***Block* β_2-receptors** in the **liver** ⇨ **↓ Glycogenolysis**.
- ***Block* β_2- receptors** in the **pancreas** ⇨ **↓ Glucagon**.

  N.B: **Glucagon hormone *used to combat* hypoglycemia** effects, ***So***; ***non-selective* β-blockers used *with caution*** in **insulin-dependent diabetic patients**.
- ***Block* β_2-receptors** in **skeletal muscles** ⇨ ***hyperkalemia***.
- **Chronic use** ☞ **↑ VLDL** (very low density lipoprotein) and **↓ HDL** (high density lipoprotein; good cholesterol) ⇨ **↑ *risk for* coronary artery disease**.
- **Propranolol *may cause* sodium** and **water retention**.

Therapeutic Uses

- **Hypertension**:
  - **β-blocking agents** (*especially* **Propranolol**) do ***not*** *usually* **cause hypotension** in **healthy individuals** *with* ***normal*** **blood pressure**.
  - **Propranolol** ***lowers*** **blood pressure** in **hypertension** by ***several different*** **mechanisms** *of* **action**:
    1) ***Decrease*** **cardiac output** (primary mechanism).
    2) ***Inhibition*** of **renin release** ***from*** the **kidney**.
    3) ***Decrease*** in **total peripheral resistance** (chronic use).
    4) ***Decrease*** **sympathetic outflow** ***from*** the **CNS**.
- **Angina Pectoris (Ischemic Heart Disease)**:
  - ***Decrease*** **cardiac work** & ***decrease*** **O_2 requirement** of **heart muscle**.
  - ***Useful*** in **chronic management** of **stable angina** (*not* variant angina).
- **Myocardial Infarction**: (due to decrease O_2 consuming)
  - As a ***protected*** *against* a **second heart attack** (prophylactic).
  - ***Reduce*** **infarct size** and **hastens recovery**.
  - ***Reduce*** the **incidence** of ***sudden*** **death** *after* **myocardial infarction**.
- **Cardiac Arrhythmias**:
  - ***Effective*** in the **treatment** of ***both*** **supraventricular** and **ventricular arrhythmias**.
- **Hypertrophic Subaortic Stenosis**:
  - **Propranolol** improve NYHA (New York Heart Association) functional class in symptomatic patients with hypertrophic subaortic stenosis.


Normal *Hypertrophic*

- **Hyperthyroidism**:
  - ***Protective*** *against* **sympathetic *stimulation*** that *occurs* in **hyperthyroidism**.
  - **Propranolol** ***inhibits*** the **peripheral conversion** of T_4 (thyroxine; less potent) to T_3 (triiodothyronine; more potent).
- **Migraine**: used as ***prophylaxis*** of **migraine headache**.
- **Anxiety Status**: ***control*** **sympathetic symptoms** (tachycardia/tremor).

Side Effects

- **Hypotension** (common).
- **Bronchospasm** (uncommon): **Propranolol** is **C/I** in **COPD** or **asthma**.
- **Arrhythmias** (uncommon): **Bradycardia** or **heart failure**.
- **Metabolic disturbances** (uncommon):
  - ↓ **glycogenolysis** and ↓ **glucagon** ***secretion*** ⇨ ↑ *incidence* of **hypoglycaemic episodes** *in* **type I diabetics** (***fasting hypoglycemia***).
  - ↑ **LDL** (low density lipoprotein; bad cholesterol) ⇨ ↑ ***risk*** *for* **coronary artery disease**.
- **Cold extremities (Raynaud's phenomenon)** (common):
  - May due to reflex peripheral vasoconstriction.
- **Male impotence** (uncommon): Mechanism is unclear.
- **CNS effects** (severity depends on lipophilicity) (common):
  - **Sleep *disturbances*** (**insomnia** and **vivid dreams** and **nightmares**), **fatigue** and **irritability**.

FDA Warning

- The **β-blockers** ***must be*** **tapered off** ***gradually***.
- **Long-term treatment** *with* **β-blocker** ⇨ ***up-regulation*** of **β-receptors**.
- ***Sudden*** **stop** of **β-blocker therapy** ⇨ ***increased*** **receptors sensitivity** and can ***worsen*** **angina** or **hypertension**.

Nadolol (Corgard®) | Timolol (Timogel®)

- **Nadolol** [NAH-doh-lole] and **Timolol** [TIM-o-lole] are a ***non-selective*** **β-blocker drugs**.
- **Nadolol** and **Timolol** are ***more potent*** than **Propranolol**.
- **Nadolol** has a ***very long*** **duration of action** with ***low*** **lipid solubility** and ***used*** in **hypertension**, **angina pectoris**, **migraine prophylaxis** and **anxiety symptoms**.
- **Nadolol** (***non-selective***) **widely** ***used*** in **esophageal varices** to ***prevent*** (prophylaxis) **bleeding** in people with **portal hypertension** caused by ***cirrhosis*** (decrease both cardiac output by β_1-blockade and splanchnic blood flow by blocking vasodilating β_2-receptors at splanchnic vasculature).
- **Timolol** ***used*** topically in the ***treatment of*** **chronic open-angle glaucoma** due to it ***reduces*** the ***production*** of **aqueous humour** in the **eye**.

Carteolol (Ocupress®) | Metipranolol (Betanol®) | Levobunolol (Betagan®)

- **Carteolol** [KAR-tee-oh-lole], **Levobunolol** [lee-voe-BYOO-noe-lole] and **Metipranolol** [met-i-PRAN-oh-lol] are a non-selective drugs ***used*** to ***treatment of*** **chronic open-angle glaucoma**.

Drugs Used in Open Angle Glaucoma

Cholinomimetics	Pilocarpine, Carbachol, Physostigmine, Echothiophate, Demecarium	*Opining trabecular meshwork; increased outflow*
α-Agonists	Non-selective; Epinephrine, Dipivefrin	*Increased outflow*
	Selective α_2; Apraclonidine, Brimonidine	*Decreased aqueous secretion*
β-blockers	Timolol, Betaxolol, Carteolol, Levobunolol, Metipranolol	*Decreased aqueous secretion*
Carbonic anhydrase inhibitors	Dorzolamide, Brinzolamide, Acetazolamide, Dichlorphenamide, Methazolamide	*Decreased aqueous secretion*
Prostaglandins	Latanoprost, Bimatoprost, Travoprost, Unoprost	*Increased outflow*

Sotalol (Betacor®)

- **Sotalol** [SOE-ta-lol] is a ***non-selective*** **β-blocker drug**.
- It is an **antiarrhythmic drug** with **Class II** (beta-adrenoreceptor blocking) and **Class III** (cardiac action potential duration prolongation; inhibit of potassium channels) ***properties***.

B: Selective β_1-adrenoceptor Antagonists

- These agents may be ***safer*** in patients who experience **bronchoconstriction** in response to **propranolol**.
- These agents may be ***preferable*** in patients with **diabetes** or **peripheral vascular disease**.

Betaxolol (Betoptic®)

- **Betaxolol** [be-TAX-oh-lol] is a ***selective*** **β_1-blocker**.
- ***Used*** **topically** to ***treatment of*** **chronic open-angle glaucoma**.
- ***Less*** **likely** to ***induce*** **bronchoconstriction** ***than non-selective*** **antagonists**.

Esmolol (Brevibloc®)

- **Esmolol** [EZ-moe-lole] is an ***ultra-short-acting*** **β_1-*selective*** **adrenoceptor antagonist**.
- It has a ***very short*** **half-life** (about 10 minutes) due to metabolism of an ester linkage.
- It is only available ***intravenously*** and it is ***used*** to **control blood pressure** or **heart rhythm** during surgery or diagnostic procedures.

Bisoprolol (Concor®)

- **Bisoprolol** [BIS-oh-PROE-lol] is a ***selective*** **β_1-blocker** (cardioselective).
- It is ***used*** in the ***management*** of **hypertension** and **heart failure**.

Nebivolol (Nebilet®)

- **Nebivolol** [ne-BIV-oh-lol] is the ***most highly selective*** **β_1-blocker** ***with*** **nitric oxide-potentiating vasodilatory effect.**
- **Nebivolol** *approximately* **3.5 times** ***more*** **β_1-selective than Bisoprolol.**
- **Nebivolol** *induce* ***releases*** of **nitric oxide** (endothelium-derived relaxing factor; EDRF) from **endothelial cells** and *causes* ***vasodilation.***
- ***C/I*** **(Contraindicated)** in ***severe*** **renal** and ***severe*** **hepatic impairment.**
- It is ***used*** as **antihypertensive** and **anti-anginal agent.**

Metoprolol (Lopressor®)

- **Metoprolol** [me-TOE-proe-lole] is a ***selective*** **β_1-blocker.**
- It is one of the ***most prescribed*** drug in the United States.
- It has ***moderately*** **lipophilic** properties ⇨ ***penetrate*** **BBB** ⇨ cause ***sleep disturbances.***
- It is ***used*** in **hypertension, angina, heart failure, acute myocardial infarction, arrhythmias, migraine prophylaxis** and **anxiety symptoms.**

Atenolol (Tenormin®)

- **Atenolol** [a-TEN-oh-lole] is a ***selective*** **β_1-blocker.**
- It has **hydrophilic** properties ⇨ ***less*** suitable in **migraine prophylaxis** *compared to* **propranolol.**
- It is ***used*** in **hypertension, angina, acute myocardial infarction** and **arrhythmias.**

C: β-adrenoceptor Antagonists with Partial Agonist Activity

- These agents usually has **Intrinsic Sympathomimetic Activity (ISA)**: This term is used particularly with **β-blockers** that can show both ***agonist*** and ***antagonist*** **effect** at **β-receptors** ⇨ cause activation of adrenergic receptors so as to produce effects similar to stimulation of the sympathetic nervous system.
- ***Partial*** **agonist activity** of these agents may be ***less*** **likely** to cause **bradycardia** and ***abnormalities*** in **plasma lipids** (not decrease plasma HDL levels) than are **antagonists.**

Acebutolol (Sectral®)

- **Acebutolol** [a-se-BYOO-toe-lole] is a ***cardioselective*** **β-blocker** with ***mild*** **ISA.**
- It is ***used*** in **hypertension** and **ventricular arrhythmias.**

Pindolol (Visken®)

- **Pindolol** [PIN-doe-lole] is a ***non-selective*** **β-blocker** with **ISA.**
- It is ***used*** in **hypertension**, may be **used *alone*** or *with* ***other*** **antihypertensive agents**, *particularly* with a **thiazide-type diuretic.**
- It also functions as a **5-HT (serotonin) receptors**, so may considered as ***augmentation therapy*** of **depression** or **premature ejaculation.**

Celiprolol (Selectol®)

- **Celiprolol** [SEE-li-proe-lole] is a **β_1-*selective*** **blocker** with ***modest*** capacity to ***activate*** **β_2-receptors**
- It may have ***less*** **bronchoconstriction** effect in asthma and *may even* ***promote*** **bronchodilatation.**

Oxprenolol (Trasicor®) | **Penbutolol** (Levatol®)

- **Oxprenolol** [ox-PREN-oh-lole] and **Penbutolol** [pen-byoo-TOH-lol] are a ***non-selective*** **β-blocker** with **ISA**, ***used*** in **hypertension**, may be **used *alone*** or *with* ***other*** **antihypertensive agents.**

D: Selective β_2-adrenoceptor Antagonists

Butaxamine or Butoxamine

- **Butoxamine** is a **research drug** ***selective*** for **β_2-receptors**, *non-available* for **clinical uses**.

3) Mixed Adrenoceptor Antagonists

Labetalol (Trandate®)

- **Labetalol** [lah-BET-a-lole] is a ***reversible*** (competitive) **adrenoceptor antagonist**.
- It is a ***non-selective*** **β-adrenergic blocker** and ***selective*** **α_1-adrenergic blocker**.
- **Labetalol potency** is ***somewhat lower than*** that of **Propranolol**.
- **Labetalol affinity** for **α-receptors** is ***less than*** that of **Phentolamine** (but **Labetalol** is α_1-selective).
- **Hypotension** *induced by* **Labetalol** is accompanied by ***less*** **tachycardia** than occurs with **Phentolamine** and ***similar*** **α-blockers**.
- ***Therapeutic uses***:
  - **Treatment** of ***chronic*** or ***acute*** **hypertension** of ***pheochromocytoma*** and ***hypertensive crisis***.
  - **Treatment** of **pregnancy-induced hypertension** *associated with* ***pre-eclampsia***.
- ***Most common side effects***: **dizziness**, **fatigue** and **nausea**.

Carvedilol (Dilatrend®)

- **Carvedilol** [KAR-ve-dil-ole] is a ***reversible*** **adrenoceptor antagonist**.
- It is a ***non-selective*** **β-adrenergic blocker** and ***selective*** **α_1-adrenergic blocker**.
- ***More potently*** at **β-receptors** than **α_1-receptors**.
- **Carvedilol** ***has benefits*** (or ***protective effects***) in **heart failure** :
  - ***Decrease*** **lipid peroxidation** and **oxidative injury** to **endothelial cells**.
  - ***Decrease*** **vascular wall** ***thickening***.
- It is ***used*** in the treatment of ***mild*** to ***severe*** **congestive heart failure** (CHF) and **hypertension**.

Choice of β-adrenergic Antagonist Drug

- **Congestive Heart Failure (CHF): Carvedilol > Metoprolol > Bisoprolol.**
- **Open-angle glaucoma: Timolol, Betaxolol > Carteolol > Levobunolol > Metipranolol.**
- **Pheochromocytoma hypertension and hypertensive crisis: Labetalol.**
- **Pregnancy-induced hypertension with pre-eclampsia: Labetalol.**
- **Migraine prophylaxis and anxiety symptoms: Propranolol > Metoprolol > Nadolol.**
- **Prevent bleeding in people with portal hypertension (cirrhosis): Nadolol > Propranolol.**
- **Most highly selective β_1-blocker with nitric oxide-potentiating vasodilatory effect: Nebivolol.**
- **Augmentation therapy of depression or premature ejaculation: Pindolol.**
- **Control blood pressure or heart rhythm during surgery: Esmolol.**
- **Effective in asthma and may even promote bronchodilatation: Celiprolol.**
- ***Note***; **African ancestry and elderly hypertensive patients: β-blockers** are ***less*** **effective**.

Drug interactions with Most β-adrenoceptor Antagonists

Pharmacokinetics Drug Interactions

Enzyme *Inhibitors* Drugs: Cimetidine, Erythromycin and **Ketoconazole.**	☞ Inhibit hepatic metabolism of β-blockers ⇨ ↑ plasma concentration of β blockers ⇨ ↑ activity of β blockers and may lead to toxicity.
Enzyme *Inducers* Drugs: Rifampicin, Phenytoin, and **Phenobarbital.**	☞ Increase hepatic metabolism of β-blockers ⇨ ↓ plasma concentration of β blockers ⇨ ↓ activity of β blockers and may lead to loss of activity.

Pharmacodynamics Drug Interactions

Sympathomimetic drugs or **drugs having α_1-agonist effect.**	☞ ↑ **Epinephrine** release ⇨ act only in **α** receptors due to **β**-receptors are blocked ⇨ enhance reflex VC effect.
Calcium channel blockers (CCB) e.g.: **Verapamil**	☞ **Verapamil** ⇨ (-ve) inotropic and (-ve) Chronotropic ⇨ when given with β-blockers ⇨ **additive effect** - Cause ⇨ Cardiac depression (bradycardia and may lead to heart block).
Non-steroidal anti-inflammatory drugs (NSAIDs) e.g.: **Indomethacin**	☞ NSAIDs inhibit formulation of prostaglandins ⇨ ↓ renal VD ⇨ ↓ renal blood flow ⇨ ↑ sodium and water retention ⇨ ↓ antihypertensive effect of **β**-blockers.
Insulin	☞ Non-selective **β**-blockers potentiate the hypoglycaemic effect of **Insulin**.

Adrenergic Neuron Blockers

4) Drugs that interfere with neurotransmitters release

Guanethidine (Ismelin®)

- **Guanethidine** [gwha-NETH-ih-deen] is an **antihypertensive drug** that reduces the release of catecholamines, such as norepinephrine.
- It acts by ***blocking the release*** of stored **norepinephrine** (NE) (replacing NE in these vesicles) ⇨ ***gradual*** depletion of NE stores in the nerve endings ⇨ ***gradual*** decrease in BP and HR.
- It is ***used*** in the treatment of ***moderate*** and ***severe*** **hypertension** and **renal hypertension**.
- ***Side effects***: **Bradycardia, orthostatic hypotension, failure of ejaculation** and **nasal congestion**.

Bretylium (Bretylol®)

- **Bretylium** [bruh-til-ee-uh m] is an **antiarrhythmic drug** that block the release of norepinephrine.
- ***Uses***: in ***emergency*** for **acute ventricular tachycardia** and **acute ventricular fibrillation**.

Reserpine (Hypoten®)

- **Reserpine** [re-SER-peen] is one of the remaining agents in this category.
- It is a **plant alkaloid** from dried root of ***Rauwolfia serpentina*** (Indian snakeroot).
- It acts by irreversibly blocks vesicular monoamine transporter (VMAT) (block Mg^{2+}/adenosine triphosphate-dependent transport) of monoamine neurotransmitters (norepinephrine, dopamine, and serotonin) from storage vesicles in the adrenergic nerve terminals in all body tissues.
- It has a ***slow onset***, a ***long duration*** of action.
- ***After discontinuation*** ⇨ The effects persist for **many days**.
- It is ***used*** in the treatment of ***mild*** **hypertension** ***but*** has largely been replaced with newer agents.
- ***Most common side effects***:
  - Diarrhea, hyperacidity and dry mouth.
  - Bradycardia and nasal congestion.
  - Anxiety and depression (***Rare***) ⇨ due to depletion of NE and serotonin in the brain.
  - Parkinsonian syndrome (***Rare***) ⇨ due to depletion of dopamine from basal ganglia.

Revision and Questions with Answers